

First Reported Live Birth Following ICSI in a Man with Combined Complete AZFb and AZFc Y-Chromosome Microdeletions and 45,X/46,XY Mosaicism

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Case Report

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Abstract

Background

Y chromosome microdeletions are the second most common genetic cause of male infertility after Klinefelter syndrome. Complete azoospermia factor b (AZFb) deletions are associated with maturation arrest at the primary spermatocyte stage and an extremely poor prognosis for biological fatherhood, with no reported success following surgical sperm retrieval. Consequently, donor sperm is generally recommended. We report what is, to our knowledge, the first successful live birth following intracytoplasmic sperm injection (ICSI) using ejaculated sperm from a man with a confirmed complete AZFb and AZFc microdeletion together with a mosaic 45,X/46,XY karyotype.

Case presentation

A couple presented with two years of primary infertility. The female partner, aged 34 years, had polyendocrine metabolic ovarian syndrome (PMOS) with a high ovarian reserve. The male partner had severe oligozoospermia, low testosterone, elevated follicle-stimulating hormone and reduced testicular volumes. Genetic investigations demonstrated a complete AZFb and AZFc Y chromosome microdeletion together with a mosaic 45,X/46,XY karyotype. Following multidisciplinary team discussion and comprehensive genetic counselling, treatment with ICSI using fresh ejaculated sperm was undertaken. Ovarian stimulation yielded 30 oocytes, of which 27 were mature. However, after prolonged laboratory preparation, only nine viable sperm were identified for injection. An initial treatment cycle resulted in no transferable blastocysts, and the remaining mature oocytes were vitrified. Subsequent management involved thawing oocytes according to the number of viable sperm available on the day of treatment. One treatment cycle was cancelled because no sperm were identified, while a later cycle proceeded successfully after rare viable sperm were recovered. Transfer of an early blastocyst and a partial morula resulted in an uncomplicated singleton pregnancy and the delivery of a healthy female infant at term.

Conclusions

This case demonstrates that exceptionally rare men with a genetic profile traditionally considered incompatible with biological fatherhood may retain sufficient residual spermatogenesis to achieve successful fertilisation and live birth. Multidisciplinary management, repeated semen assessment, tailored oocyte warming according to sperm availability, and individualised laboratory planning were fundamental to the successful outcome. This report expands the current understanding of the reproductive potential associated with complete AZFb and AZFc microdeletions and highlights the importance of personalised management in selected patients.

Background

Male factor infertility contributes to approximately 40–50% of infertile couples¹, with isolated male factor accounting for around 20% of cases¹. After Klinefelter syndrome, Y chromosome microdeletions represent the second most common identifiable genetic cause of severe spermatogenic failure²³. Microdeletions involving the azoospermia factor (AZF) region on the long arm of the Y chromosome disrupt genes essential for normal spermatogenesis and are identified in approximately 5–15% of men with non-obstructive azoospermia or severe oligozoospermia³.

The AZF region comprises three principal subregions (AZFa, AZFb and AZFc), each associated with distinct histological phenotypes and reproductive outcomes. Complete AZFb deletions are classically associated with meiotic

arrest at the primary spermatocyte stage and have consistently been associated with an extremely poor prognosis for sperm retrieval⁴. Current international guidelines generally do not recommend surgical sperm retrieval in men with complete AZFb deletions because published series report virtually no successful retrieval of mature sperm^{5 6}. Consequently, donor sperm is frequently recommended for family building⁷.

We report what is, to our knowledge, the first successful live birth achieved using ejaculated sperm from a man with a documented complete AZFb and AZFc microdeletion in association with mosaic 45,X/46,XY karyotype. The case highlights the importance of multidisciplinary decision-making and an individualised treatment strategy in carefully selected patients.

Case Presentation

A couple was referred to our tertiary fertility centre following two years of primary infertility. The female partner was 34 years old and otherwise fit and healthy. She had features consistent with polyendocrine metabolic ovarian syndrome (PMOS), including polycystic ovarian morphology on ultrasound and clinical hyperandrogenism manifested by severe acne, although she reported regular menstrual cycles⁸. Her anti-Müllerian hormone (AMH) concentration was 48.2 pmol/L, consistent with a high ovarian reserve^{9 10 11}.

The male partner was 32 years old, otherwise fit and well apart from previous orthopaedic surgery for lower limb asymmetry. He had no significant medical history, no history of cryptorchidism, testicular trauma or gonadotoxic treatment.

Semen analysis demonstrated severe oligozoospermia. Following density-gradient preparation, only a very small number of motile spermatozoa were identified (5 grade A, 6 grade B, 4 grade C and 10 grade D sperm in a final preparation volume of 20 µL). Despite the extremely poor semen quality, the sample was considered technically suitable for ICSI¹².

Endocrine assessment demonstrated primary testicular dysfunction¹³, with a serum testosterone concentration of 5.3 nmol/L, follicle-stimulating hormone (FSH) of 12.2 IU/L and luteinising hormone (LH) of 4.2 IU/L. Scrotal ultrasonography demonstrated structurally normal testes with reduced testicular volumes of 7.5 mL and 10 mL.

Genetic investigations were undertaken at United Kingdom Accreditation Service (UKAS) laboratories through a PCR-based Y chromosome microdeletion assay and karyotype. These revealed a complete AZFb and AZFc Y chromosome microdeletion together with a mosaic 45,X/46,XY karyotype (mosaic Turner syndrome). The couple underwent detailed genetic counselling. They were informed that any male offspring conceived would inherit the Y chromosome microdeletion and would therefore be expected to experience infertility. They were also counselled regarding the small theoretical risk associated with the combination of the paternal genetic diagnoses, including the possible slightly increased aneuploidy risk in the offspring due to mosaic 45,X and the not widely accepted increased Turner syndrome risk due to Y chromosome deletions^{14 15}. These risks are difficult to define, particularly due to the low fertility in these cases and that limited research primarily focuses on Turner syndrome and 45,X/46,XX Turner syndrome and may be influenced by maternal egg health factors that are not relevant in this case.

The case was discussed at the specialist male infertility multidisciplinary team (MDT) meeting, involving reproductive medicine specialists, urological surgeons / andrologists, endocrinologists, genetic counsellors, and senior embryologists. Although the genetic findings suggested a very poor prognosis, the presence of rare motile sperm within the ejaculate led the MDT to recommend proceeding with ICSI using freshly ejaculated sperm.

The female partner underwent controlled ovarian stimulation using a GnRH antagonist protocol with human menopausal gonadotrophin (Menopur) 150 IU daily. After 10 days of stimulation, a high ovarian response was achieved (Fig. 1). In view of the increased risk of ovarian hyperstimulation syndrome (OHSS), final oocyte maturation was triggered with a GnRH agonist and a freeze-all strategy was planned^{16 17 18}.

Thirty oocytes were retrieved, of which 27 were mature (metaphase II) and suitable for ICSI. Extensive laboratory preparation of the semen sample was required. Two experienced embryologists independently examined the processed sample for approximately two hours before identifying only nine motile spermatozoa suitable for injection. The post-preparation sample closely resembled the appearance of a poor-quality testicular sperm extraction (TESE) specimen, with scarce viable sperm.

Due to the limited number of available sperm, only nine mature oocytes were injected. Two oocytes fertilised normally; however, neither embryo progressed to a viable blastocyst suitable for transfer or cryopreservation. The remaining 18 mature oocytes were vitrified for future treatment.

Following review by the MDT, an individualised strategy was developed. Rather than warming all remaining oocytes simultaneously, it was agreed that oocytes would be thawed gradually according to the number of viable sperm identified on the day of treatment. This approach aimed to minimise wastage of oocytes while allowing repeated attempts using fresh ejaculated sperm.

Three months later, the couple returned for their first frozen oocyte warming cycle. The female partner commenced endometrial preparation using transdermal oestrogen¹⁹. However, despite extensive laboratory assessment, no viable spermatozoa could be identified in the ejaculate on the day of treatment, and the cycle was cancelled before oocyte warming.

One month later, a further attempt was undertaken. Endometrial preparation was repeated using transdermal oestrogen patches. On this occasion, following prolonged examination of the semen sample, sufficient viable sperm were identified for ten ICSI injections. Two experienced embryologists again spent approximately two hours each preparing and searching the specimen because of the exceptionally poor sperm quality.

Ten vitrified oocytes were warmed successfully and underwent ICSI. Four oocytes fertilised normally. Embryo culture resulted in the development of an early blastocyst and a partial morula, both of which were transferred during the same treatment cycle (Fig. 2). Luteal phase support was provided with standard vaginal progesterone^{19 20}.

The patient conceived following embryo transfer and experienced an uncomplicated singleton pregnancy. She subsequently delivered a healthy female infant at term with a birth weight of 3,856 g.

Following delivery, the couple received further counselling regarding future family planning. In view of the unpredictable nature of sperm production and the possibility of progressive deterioration to complete azoospermia associated with the patient's underlying complete AZFb and AZFc microdeletion²¹, they were advised not to delay further fertility treatment if additional children were desired. The MDT recommended further oocyte warming cycles while viable ejaculated sperm remained available, with the aim of creating and cryopreserving embryos for future use. Although only a small number of embryos with modest developmental potential were anticipated, making immediate fresh embryo transfer an attractive option, postponing treatment until the couple were ready to attempt a second pregnancy carried a substantial risk that sperm production could deteriorate further, potentially resulting in complete azoospermia. The couple were therefore counselled regarding this balance between transferring embryos fresh and preserving future reproductive potential through embryo cryopreservation. The option of sperm cryopreservation during future occasions when viable ejaculated sperm could be identified was also discussed; however, they were advised

that freeze-thawing may further compromise the function of an already severely impaired sperm sample²². Testosterone replacement therapy was recommended once completion of the family's reproductive plans had been achieved.

Discussion and Conclusions

Y chromosome microdeletions involving the AZF region represent one of the most important genetic causes of severe male factor infertility²³. Among these, complete AZFb deletions are associated with an extremely poor reproductive prognosis because spermatogenesis typically arrests at the primary spermatocyte stage, resulting in non-obstructive azoospermia or exceptionally severe spermatogenic failure. Published evidence consistently demonstrates an almost negligible likelihood of successful sperm retrieval in men with complete AZFb deletions, and current clinical practice generally discourages surgical sperm retrieval in these patients because of the very low probability of identifying mature sperm²¹. Consequently, donor sperm is frequently recommended as the most realistic reproductive option^{5 6}.

The present case is therefore highly unusual. Despite a confirmed complete AZFb and AZFc microdeletion together with a mosaic 45,X/46,XY karyotype, rare viable spermatozoa were repeatedly identified in the ejaculate, allowing ICSI treatment to be performed without surgical sperm retrieval. Following carefully planned treatment, the couple achieved the live birth of a healthy female infant born at term. To the best of our knowledge, this represents the first reported live birth achieved using ejaculated sperm from a man with this specific genetic profile. Although this exceptional outcome should not alter current counselling regarding the generally poor prognosis associated with complete AZFb deletions, it demonstrates that biological paternity may occasionally be achievable in patients with demonstrable residual spermatogenesis.

One of the major learning points from this case is the importance of multidisciplinary team (MDT) management in complex male factor infertility. Clinical decision-making required close collaboration between reproductive medicine specialists, andrologists, embryologists, endocrinologists and clinical geneticists. The reproductive implications of the patient's genetic diagnosis, the likelihood of progressive deterioration in spermatogenesis, the expected laboratory challenges, and the reproductive risks for future offspring were considered collectively before treatment was undertaken. This collaborative approach enabled an individualised treatment strategy that balanced realistic expectations with the couple's wish to pursue treatment using their own gametes.

The laboratory management was equally critical to the successful outcome. The extreme scarcity of viable sperm meant that conventional treatment planning was inappropriate. Rather than warming all vitrified oocytes at once, the MDT adopted a flexible strategy whereby the number of oocytes warmed was determined by the number of viable sperm identified on the day of treatment. This avoided unnecessary loss of oocytes during cycles in which sperm were absent or insufficient while preserving opportunities for future treatment attempts. Indeed, one scheduled treatment cycle was appropriately cancelled when no viable sperm were identified, preventing unnecessary oocyte thawing. When sufficient sperm became available one month later, oocyte warming and ICSI proceeded successfully. We believe this pragmatic approach represents an important management strategy for patients with extremely limited and unpredictable sperm availability and may be applicable to similar cases.

Another important consideration was the decision to use fresh ejaculated sperm whenever available. Given the extremely poor quality and very limited number of sperm recovered after prolonged laboratory preparation, cryopreservation was considered unlikely to preserve adequate sperm function and may have resulted in further deterioration following freeze-thawing. In contrast, using freshly ejaculated sperm maximised the opportunity for successful fertilisation. The appearance of the processed sample closely resembled that of a poor-quality testicular

sperm extraction specimen despite being obtained from the ejaculate, highlighting the severity of the underlying spermatogenic impairment.

Comprehensive counselling before and after treatment formed an integral component of management. The couple received detailed genetic counselling regarding the inheritance of the Y chromosome microdeletion, including the expectation that any male offspring would inherit the deletion and would likely experience infertility. They were also counselled regarding the potential reproductive implications of the mosaic 45,X/46,XY karyotype. Following successful treatment, future reproductive planning was again individualised. In view of the unpredictable nature of sperm production and the possibility of progression to complete azoospermia, the couple were advised not to delay further treatment if additional children were desired. Continued oocyte warming tailored to sperm availability was recommended, together with consideration of sperm cryopreservation during future occasions when viable sperm could be identified. Testosterone replacement therapy was deferred until completion of the family's reproductive plans because of its potential adverse effects on spermatogenesis.

This case demonstrates that even in patients with genetic findings traditionally considered incompatible with successful biological fatherhood, carefully selected individuals may retain sufficient residual spermatogenesis to achieve fertilisation and live birth. Although current evidence and clinical guidelines regarding complete AZFb deletions should remain unchanged, our experience highlights the importance of individualised assessment whenever rare ejaculated sperm are present. Successful outcomes depend not only on the presence of viable sperm but also on meticulous laboratory techniques, flexible treatment planning, comprehensive genetic counselling and close multidisciplinary collaboration.

In conclusion, we report what is, to the best of our knowledge, the first published case of a healthy live birth at term following ICSI using ejaculated sperm from a man with a confirmed complete AZFb and AZFc microdeletion together with a mosaic 45,X/46,XY karyotype. This case expands the current understanding of the reproductive potential associated with these rare genetic abnormalities and illustrates how personalised multidisciplinary management can optimise the chance of success in patients who would traditionally be considered unsuitable for biological parenthood.

Declarations

Ethics committee approval was not required for this retrospective case report in accordance with institutional policy and local regulations. Written informed consent for publication of the clinical details contained in this report was obtained from the couple. The authors declare that they have no competing interests.

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Author Contribution

AS contributed to patient management, data collection, literature review, manuscript drafting and revision. SJ contributed to embryology data collection, interpretation of laboratory findings, manuscript drafting and revision. SS contributed to the genetic investigations, interpretation of genetic findings, and critical revision of the manuscript. TS contributed to patient management, literature review, and critical revision of the manuscript. VM contributed to multidisciplinary management of the patient and critical revision of the manuscript. RM contributed to study conception and design, patient management, supervision of the project, and critical revision of the manuscript. NT

conceived the study, managed the patient, performed the literature review, interpreted the clinical findings, drafted the manuscript, prepared the figures, supervised the project, and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Figures

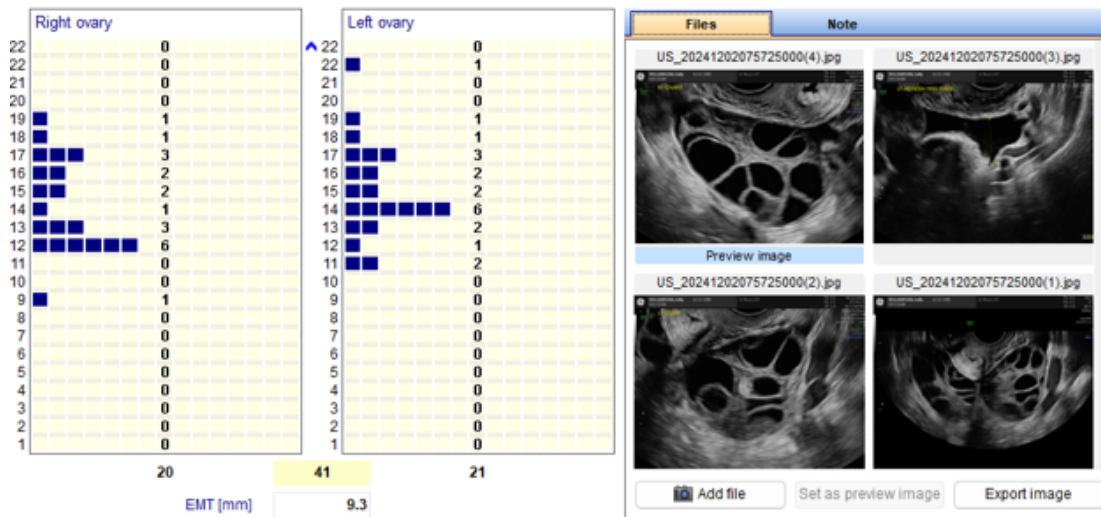


Figure 1

High ovarian response on the 10th day of stimulation- US Scan images and Folliculogram

Table representation		Graphical representation		Survived representation						
Dev. exp.	$\frac{d}{2}$	SP	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	
Dev. ID	Time		17/03/2025	18/03/2025	19/03/2025	20/03/2025	21/03/2025	22/03/2025	23/03/2025	
1	27406	ICSI	SP I							
2	27407	ICSI	SP I							
3	27408	ICSI	SP I							
4	27409	ICSI	SP I							
5	27410	ICSI	SP I							
6	27411	ICSI	SP I							
7	27412	ICSI	SP I							
8	27413	ICSI	SP I							
9	27414	ICSI	SP I							
10	27415	ICSI	SP I							

Figure 2

Embryo development following intracytoplasmic sperm injection (ICSI).