Karyotypic abnormalities and Y chromosome microdeletions: How do these impact in vitro fertilization outcomes, and how common are they in the modern in vitro fertilization practice?

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Objective: To examine the outcomes of in vitro fertilization with intracytoplasmic sperm injection (IVF-ICSI) in couples in whom the male partner has a karyotypic abnormality or Y chromosome microdeletion (YCM).
Design: Retrospective cohort.
Setting: Single infertility center.
Patient(s): Couples treated with IVF-ICSI from January 2014 to April 2019 with male factor infertility, sperm concentration of $<5 \times 10^6$ sperm/mL, and results for karyotype and/or YCM panel.
Intervention(s): In vitro fertilization with intracytoplasmic sperm injection.
Main Outcome Measure(s): In couples in whom the male partner had a karyotypic abnormality or YCM: live birth rate/ongoing pregnancy rate, lack of partner sperm for fertilization, complete fertilization failure, cycle cancellation, and no embryos for transfer. The prevalence of karyotypic abnormalities and YCMs in the IVF population was calculated.
Result(s): The live birth rate/ongoing pregnancy rate for those using partner sperm was 51.4% per transfer. However, 8.5% of cycles that intended to use partner sperm and 22.2% of cycles that intended to use surgically extracted partner sperm had no sperm available. Of cycles that created embryos with partner sperm, 12.5% had no embryo to transfer. The prevalence of karyotypic abnormalities was similar to previous reports (6.0%), while that of YCMs was lower (4.4%). Azoospermia factor a and b mutations were not represented in this population.
Conclusion(s): It is reasonable to attempt IVF-ICSI with partner sperm in patients with genetic causes of male infertility. Patients should be counseled regarding the possibility of no sperm being available from the male partner, poor/failed fertilization, and genetic implications for potential offspring. Contingency plans, including IVF with donor sperm backup or oocyte cryopreservation, need to be made for these scenarios. (Fertil Steril Rep® 2021;2:300–7. ©2021 by American Society for Reproductive Medicine.)
Key Words: Male infertility, IVF, karyotype, Y chromosome microdeletion

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Up to 15% of couples experience infertility, which is defined as the inability to conceive after 1 year of unprotected intercourse (1, 2). Male factor infertility is identified as the primary cause in approximately 20% of infertile couples and as a contributing factor in another 30%–40% of couples (1). Of the various underlying causes of male factor infertility, genetic abnormalities are known to play a significant role, particularly among patients with azoospermia or severe oligospermia. Previous literature has suggested that approximately 6% of infertile men will be found to have karyotypic abnormalities and 13% of those with nonobstructive azoospermia or severe oligospermia will have a Y chromosome microdeletion (YCM) (1). Both the American Society for Reproductive Medicine and the American Urological Association recommend performing a karyotype and YCM assay in patients with a sperm concentration of $<5 \times 10^6$ spermatozoa/mL (1, 3).

Klinefelter syndrome (47,XXY) is the most common genetic cause of male infertility (4–6). The infertility associated with Klinefelter syndrome is secondary to impaired spermatogenesis due to progressive hyalinization, fibrosis, and degeneration of germ cells and Sertoli cells. This leads to severe oligospermia or azoospermia and hypergonadotropic hypogonadism (6). Despite these challenges, sperm can be found in up to 69% of men with Klinefelter syndrome using microsurgical testicular sperm extraction (microTESE) techniques (5). In a large meta-analysis of over 1,200 patients with Klinefelter syndrome, the surgical sperm retrieval rate was found to be approximately 44% per testicular sperm extraction cycle (7). After undergoing in vitro fertilization with intracytoplasmic sperm injection (IVF-ICSI) in these same patients, the live birth rate (LBR) was found to be 43% (95% confidence interval, 34%–53%) (7). However, additional outcomes such as failed fertilization and embryologic development were not reported.

Y chromosome microdeletions in the azoospermia factor (AZF) region can also result in significantly impaired or absent sperm production. The AZF region on the long arm of the Y chromosome contains genes that encode key proteins involved in sperm production and development (5, 6). These genes are organized into three different locations, entitled "a," "b," and "c" (6). Microdeletions involving the *AZFa* or *AZFb* regions result in complete loss of spermatogenesis (5). Even after a thorough testicular microdissection, no sperm will be found. For those men with microdeletions limited to the *AZFc* region, however, sperm can be retrieved in up to 70% of patients via microTESE (8). Studies on the fertility outcomes in men with AZFc microdeletions are limited given their small sample sizes. One study examined 225 patients with AZFc microdeletions, 60 of whom underwent ICSI. The resulting clinical pregnancy rate was 28% (9). In a smaller study of only 11 patients with AZFc microdeletions and mature sperm available for ICSI, the clinical pregnancy rate was found to be higher (45%), and the LBR was reported to be 36% (10).

While researchers have attempted to understand the genetic factors associated with male factor infertility for decades, it remains a challenging condition to study. Given that male infertility is not a reportable disease and is primarily treated in the outpatient setting, there is limited large-scale data that may offer insight into the prevalence of genetic abnormalities and reproductive outcomes of these affected men (11). Similarly, since infertility care is often not covered by insurance, there are few claims to track diagnoses and treatments (11). Therefore, prior reports of karyotypic abnormalities and YCMs in couples with male factor infertility are limited by small sample sizes and may differ from those seen in the modern clinical infertility setting (12–17). Furthermore, there are few studies examining the fertility outcomes in these men who subsequently undergo IVF. Our study seeks to more comprehensively evaluate IVF outcomes in this patient population and estimate the prevalence of karyotypic abnormalities and YCMs within our IVF population.

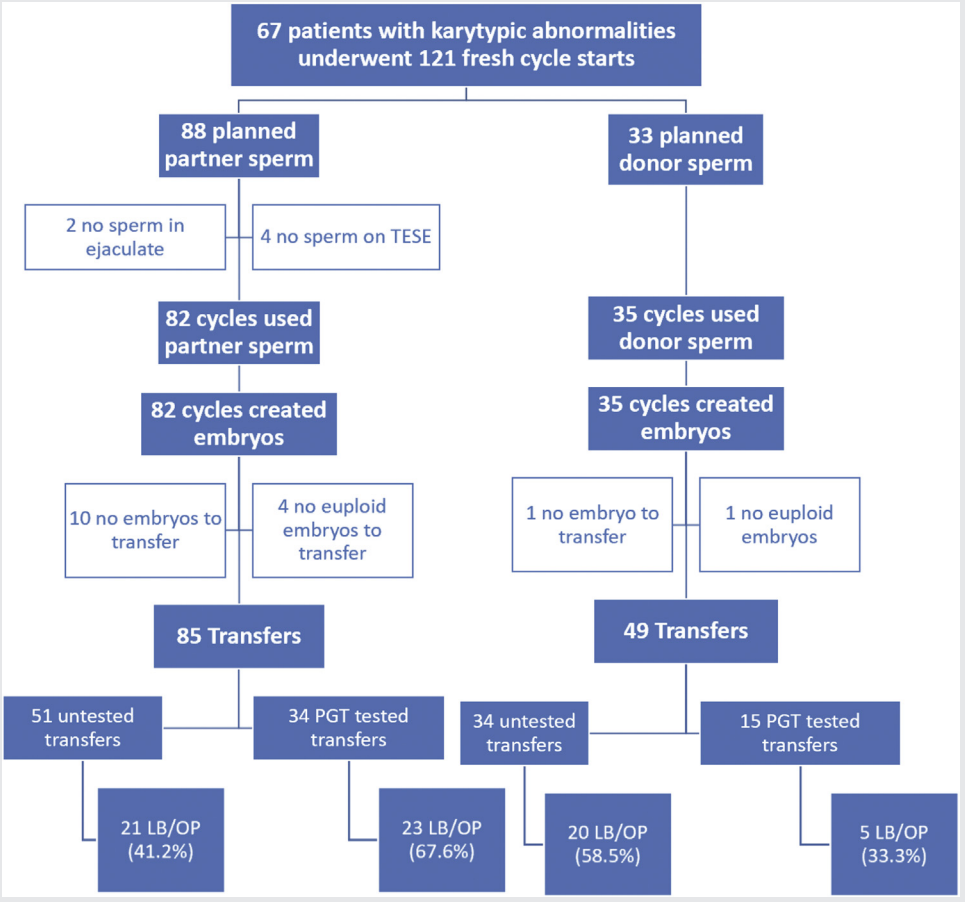
MATERIALS AND METHODS

This is a retrospective cohort study performed with Institutional Review Board approval (Advara CIRBI, Pro00027148) of patients treated with IVF-ICSI at Shady Grove Fertility from January 2014 to April 2019 with a diagnosis of "male infertility" assigned by the physician in the electronic medical record. Records were reviewed to identify those who had a karyotype and/or YCM panel performed or who had a known diagnosis of a karyotypic abnormality or YCM. Those whose initial semen analysis demonstrated azoospermia or severe oligospermia (concentration of $<5 \times 10^6$ sperm/mL) or in whom outside records indicated azoospermia or severe oligospermia were included. Male patients with a karyotypic abnormality or YCM were identified within this population. The prevalence of karyotypic abnormalities and YCMs was calculated. Men with known obstructive azoospermia were excluded. The cycles of IVF-ICSI performed in those with karyotypic abnormalities or YCMs were examined to describe cycle outcomes including cycle cancellations, lack of partner sperm for fertilization, failed fertilization, poor embryo development, and LBR/ongoing pregnancy rate (OPR) per transfer. Ovarian stimulation protocol was selected by the couple's reproductive endocrinologist based on clinical evaluation and history. All oocytes were fertilized with ICSI due to the diagnosis of male factor infertility. Surgical sperm extraction was performed in-cycle whenever possible.

RESULTS

A total of 7,341 male partners of couples undergoing IVF-ICSI with a diagnosis of "male infertility" were screened, and 1,141 unique male patients with severe oligospermia (sperm concentration of $<5 \times 10^6$ /mL) or azoospermia were included. Of these patients, 390 had azoospermia, 371 had very severe oligospermia (1 up to 1×10^6 /mL), 377 had severe oligospermia (1×10^6 to $<5 \times 10^6$ /mL), and 3 did not have semen analyses available. Of the 1,141 unique patients, 1,118 men had karyotype results, and 849 had YCM panel results. These numbers were used for prevalence denominators so as not to artificially lower the prevalence by including those who did not complete the genetic studies. Of the 1,118 patients, 67 (6.0%) had abnormal karyotypes, and 37 of 849 patients (4.4%) had a YCM. Thus, in this population, 9.1% (104/

FIGURE 1



Summary diagram of the outcomes of in vitro fertilization with intracytoplasmic sperm injection in 67 couples in whom the male partner had a karyotypic abnormality.

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1,141) of all patients had a karyotypic abnormality or YCM. There were two patients who had both karyotypic abnormalities of the Y chromosome and YCM. These two were counted as having a karyotypic abnormality, as the gross chromosomal abnormality was the cause of the YCM. In addition, 14 of 1,118 patients (1.3%) had chromosome 9 inversions, considered to be normal variants. These patients were not included in our "abnormal karyotype" cohort. This prevalence is consistent with the previously reported prevalence of chromosome 9 inversions in 1%–1.65% of the general population (18). The prevalence of karyotypic abnormalities and YCMs by semen analysis result is represented in Supplemental Table S1 (available online). A higher prevalence of karyotypic abnormalities was seen with increasing severity in semen analysis abnormalities, whereas the highest prevalence of YCMs was seen in those with very severe oligospermia (Supplemental Table S1). Approximately half (47.8%) of all patients with karyotypic abnormalities presented with azoospermia. Most patients with YCMs presented with very severe oligospermia, defined as 1 sperm/mL up to 1×10^6 sperm/mL (51.4%), but over a third presented with azoospermia (Supplemental Table S2).

Karyotypic Abnormalities

The distribution of karyotypic abnormalities (n = 67) is shown in Supplemental Table S3. The most common karyotypic abnormalities were Klinefelter syndrome (40.3%), balanced translocations (17.9%), Robertsonian translocations or derivative chromosomes (11.9%), and Y chromosome abnormalities (10.4%).

IVF sperm source, fertilization, and embryo development. Of the 121 fresh cycle starts in those with karyotypic abnormalities, 88 intended to use partner sperm for embryo creation (Fig. 1). Of the 88 cycles, 6 (6.8%) had no partner sperm available: 2 of 67 cycles that planned to use ejaculated partner sperm had no sperm in the ejaculate, and 4 of 21 cycles had no sperm on surgical extraction. In the four cycles with no sperm on surgical extraction, two resulted in cycle cancellation, and two resulted in oocyte cryopreservation. All four of these patients had Klinefelter syndrome. The two cycles with no sperm in the ejaculate were in the same patient who had a Robertsonian translocation (45,XY,-der(13;14)(q10;q10)) and was azoospermic. No surgical sperm extraction was attempted, and he and his partner were

TABLE 1

Outcome of embryos created with partner sperm by karyotypic abnormality.

Karyotype abnormality	No. of patients	No. transfers performed	LBR/OPR untested	LBR/OPR euploid
Klinefelter syndrome	16	21	50.0% (8/16)	60.0% (3/5)
Mosaic Klinefelter	2	5	-	60.0% (3/5)
Balanced translocation	11	10	33.3% (1/3)	85.7% (6/7)
Derivative chromosome	7	9	100.0% (1/1)	62.5% (5/8)
Y chromosome Issue	6	20	20.0% (3/15)	60.0% (3/5)
47,XYY	5	10	40.0% (4/10)	-
Chromosome inversion	2	3	-	100.0% (3/3)
Marker chromosome	1	2	100.0% (2/2)	-
Additional material of unknown origin	1	1	-	0% (0/1)
46XX/46XY	1	3	33.3% (1/3)	-
Isodicentric chromosome	1	1	100.0% (1/1)	-
Total	**53**	**85**	**41.2% (21/51)**	**67.6% (23/34)**

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prepared to use backup donor sperm in the likely event that no sperm was available in his ejaculate. Thus, the oocytes from these two cycles were fertilized with backup donor sperm. There were no cycles in those with karyotypic abnormalities, for whom partner sperm was available for ICSI, that resulted in complete fertilization failure.

Ultimately, 82 cycles in 53 patients with karyotypic abnormalities created embryos with partner sperm. However, 10 cycles (12.2%) resulted in no transfer due to poor embryologic development, and another 4 (4.9%) had no euploid embryos to transfer based on preimplantation genetic testing (PGT) (Fig. 1). The 10 cycles with poor embryologic development occurred in patients with Klinefelter syndrome (1), balanced translocation (1), additional genetic material of unknown origin (1), and derivative chromosome (2). In the cycles with all PGT abnormal embryos, three of the four were distributed between two couples. The male partner in both cases had the same derivative chromosome: 45, XY, der (13;14)(q10;q10). In the fourth cycle, the male partner had a balanced translocation.

There was a cumulative total of 85 transfers in 42 patients who had karyotypic abnormalities and used partner sperm for embryo creation (Table 1). The overall LBR/OPR per transfer in those using partner sperm was 51.8% (44/85). When only first transfers were examined, the LBR/OPR per transfer was 50.0% (21/42). Moreover, 60.0% of all transfers used embryos that had not been screened with PGT. The LBR/OPR in those screened with PGT was 67.6%.

Surgically extracted sperm. There were 21 surgically extracted sperm cycles in 16 patients with karyotypic abnormalities, which resulted in 16 transfers in 11 couples (Table 2). Of the 21 cycles, 2 TESE and 4 microTESE cycles used frozen sperm. The other 15 cycles were performed fresh, in-cycle. In addition to the four cycles that had no sperm at time of surgical procedure, there were an additional two that had poor embryologic development so no embryo was transferred and one that had all abnormal embryos on PGT. Approximately two-thirds (62.5%) of surgical procedures were in those with Klinefelter syndrome. The cumulative LBR/OPR per transfer in those who used surgically extracted sperm was 62.5% (10/16).

Use of donor sperm. Eleven couples attempted pregnancy with both partner and donor sperm: Klinefelter syndrome (4), XYY (2), balanced translocation (2), derivative chromosome (2), and Y chromosome issue (1). Of the 11, 3 attempted with donor sperm first: 2 of the 3 underwent multiple failed therapeutic donor insemination (TDI) cycles, while the third had all aneuploid embryos in an IVF cycle. The first two went on to have an LB/OP with partner sperm and IVF, while the third had two LB/OP from donor sperm IVF. Of the eight who attempted partner sperm first, six had at least one LB/OP with donor sperm, and 1 had an LB/OP with partner sperm. Fourteen patients with karyotypic abnormalities used only donor sperm: Klinefelter syndrome (11), balanced translocation (1), derivative chromosome (1), and Y chromosome issue (1). Eight of the 14 first attempted TDI, and two had an LB/OP as a result of TDI. All 14 eventually went on to have an LB/OP from IVF.

Y Chromosome Microdeletions

All 37 YCMs identified during genetic testing were found to be in azoospermic factor c (AZFc) only.

IVF sperm source, fertilization, and embryo development. Of the 66 fresh cycle starts in those with YCMs, 53 intended to use partner sperm for embryo creation (Fig. 2). However, 6 of 53 (11.3%) cycles had no partner sperm available. Thirty-eight cycles planned to use ejaculated partner sperm: in one, the patient was unable to produce a specimen, and in another, there was no sperm in the ejaculate. These two cycles resulted in oocyte cryopreservation, and oocytes were eventually fertilized with partner sperm. Four of 15 cycles had no sperm at the time of surgical sperm extraction. Two of these cycles resulted in the immediate use of backup donor sperm, while the other two resulted in oocyte cryopreservation. One of the two couples who vitrified oocytes was ultimately able to use partner sperm, while the other used donor sperm for fertilization. Of the 47 cycles that ultimately used partner

TABLE 2

Outcomes of surgically extracted sperm cycles by genetic abnormality.

Abnormality (No. of patients)	PESA cycles	PESA cycle and transfer outcome	TESA cycles	TESA cycle and transfer outcome	TESE cycles	TESE cycle and transfer outcome	MicroTESE cycles	MicroTESE cycle and transfer outcome
Klinefelter syndrome (10)	-	-	1	No sperm cycle cancelled	-	-	13	No sperm cycle cancelled, no sperm oocyte cryopreservation x2, no embryo development x1, LB/OP x 6, SAB x1, biochemical x1, hCG Neg x2
Balanced translocation (2)	-	-	-	-	2	All embryos aneuploid, hCG Neg x1	-	-
Derivative chromosome (2)	1	LB x1	-	-	1	LB x1	-	-
47,XYY (1)	-	-	-	-	1	Twin LB, hCG Neg x1	-	-
Y chromosome issue (1)	-	-	1	No embryo development	1	LB x1	-	-
YCM (12)	-	-	-	-	7	Twin LB x2, SAB x1, hCG Neg x5	8	No sperm oocyte cryopreservation x2, no sperm donor backup, fertilization failure x1, hCG Neg x3

Note: PESA = percutaneous epididymal sperm aspiration; TESA = testicular sperm aspiration; TESE = testicular sperm extraction; MicroTESE = microscopic testicular sperm extraction; YCM = Y chromosome microdeletion; LB/OP = live birth/ongoing pregnancy; SAB = spontaneous abortion; hCG Neg = negative pregnancy test.

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sperm, there was one cycle that resulted in complete fertilization failure. This patient had undergone a microTESE procedure. After the fertilization failure, he underwent another two procedures and was able to create one embryo from each. However, neither embryo resulted in a pregnancy.

Ultimately, 46 cycles in 28 patients with YCMs successfully created embryos with partner sperm. However, one cycle (2.2%) resulted in no transfer due to poor embryologic development, and another one (2.2%) had no euploid embryos to transfer (Fig. 2). The cumulative LBR/OPR per transfer in those with YCM using partner sperm was 50.8% (30/59). When looking at first transfers only, the LBR/OPR was 46.4% (13/28) per transfer. Moreover, 86.4% of all transfers used embryos that had not been screened with PGT. The LBR/OPR in those that screened with PGT was 37.5% (3/8).

Surgically extracted sperm. There were 15 surgically extracted sperm cycles in 12 patients with YCMs and 11 transfers performed in 9 couples. All procedures were performed fresh, in-cycle. The cumulative LBR/OPR per transfer was 18.2% (2/11). Table 2 describes the surgical procedures performed and the associated cycle and transfer outcomes.

Use of donor sperm. There were four couples with YCMs who attempted pregnancy with both partner and donor sperm. Three attempted with partner sperm before moving on to donor sperm. All four ultimately had an LB/OP with the use of donor sperm (two from TDI and two from IVF). Eight couples with YCM used only donor sperm, but three had attempted to retrieve partner sperm and had no sperm on microTESE. Seven of eight went on to have at least one LB/OP with the use of donor sperm. All were IVF pregnancies. The eighth has not yet transferred any embryos created with donor sperm.

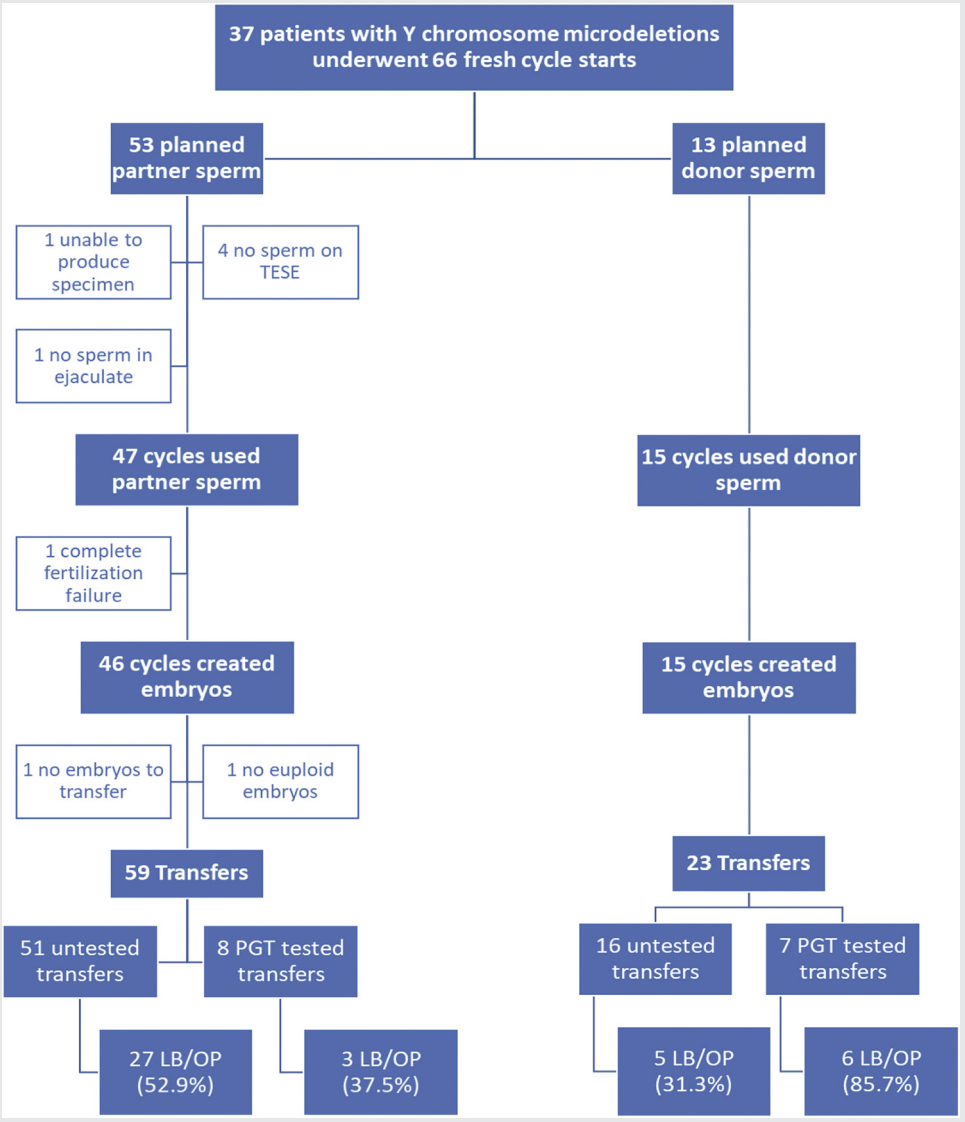
Overall Population

In the whole population of 104 couples with male genetic abnormalities, 187 fresh IVF cycles and 216 transfers were performed. However, 8.5% (12/141) of cycles that intended to use partner sperm and 22.2% (8/36) of cycles that intended to use surgically extracted sperm had no sperm available. A total of 144 (66.7%) transfers in 70 couples from 113 fresh cycles ultimately used partner sperm in embryo creation and had a cumulative LBR/OPR of 51.3%. Transfers in 20 couples who used surgically extracted sperm for embryo creation had an LBR/OPR per transfer of 44.4% (12/27).

When the female partners were examined, the mean age at fresh cycle start was 33.4 years (standard deviation [SD], 4.3 years). When those that used donor egg were excluded, the mean age at fresh cycle start was 33.1 years (SD, 4.0). Of the 104 female partners, 94.2% were nonsmokers. The mean female body mass index was 27.1 kg/m^2 (SD, 5.4), with a median of 26.3. Of the 104 couples, 78 (75%) had a single infertility diagnosis of male infertility. Female infertility diagnoses included diminished ovarian reserve (10), polycystic ovary syndrome/ovulatory disorders (9), tubal factor (6), uterine factor (2), and endometriosis (2). Three patients had multiple female infertility diagnoses.

Cycles with no embryo available for transfer. There were 16 cycles in 10 couples that, despite having partner sperm available for fertilization, resulted in no embryo to transfer, due to

FIGURE 2



Summary diagram of the outcomes of in vitro fertilization with intracytoplasmic sperm injection in 37 couples in whom the male partner had a Y chromosome microdeletion.

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either poor embryologic development (n = 11) or having all abnormal embryos on PGT (n = 5). Two of these cycles were in those with YCMs, while the remaining 14 were in those with karyotypic abnormalities. In these 10 couples, the mean female age at cycle start was relatively young (33.4 years), and the median female age was nearly identical at 33.0 years. In these patients, the mean female body mass index was 26.4 kg/m^2, with a median of 25.6. The mean number of metaphase II oocytes retrieved in these cycles was 13.0 oocytes. The mean and median percent fertilization for the 16 cycles were 58% and 61%, respectively, which were lower than the goal of $\geq$70%. The mean female age in the five couples with all abnormal embryos was 34.4 years, and the median age was 33.0 years. One particular couple in whom the male partner had a derivative chromosome accounted for 6 of the 16 cycles that resulted in no transfer. This couple ultimately had a live birth with the use of donor egg and partner sperm. When this couple was excluded, the mean female age at cycle start was even lower (33.2 years) with a median age of 31.0 years. Seven of the 10 couples had no additional diagnoses other than male infertility, while the remaining three couples each had an associated female infertility diagnosis of diminished ovarian reserve, endometriosis, or polycystic ovary syndrome/ovulatory disorder. These data suggest that, in most but not all cases, it was likely the male factor, rather than female factor, that resulted in no embryos to transfer.

DISCUSSION

It is reasonable to attempt the use of partner sperm in those with karyotypic abnormalities or YCM given the overall LBR/OPR of 51.4% per transfer. However, 8.5% (12/141) of cycles that intended to use partner sperm and 22.2% (8/36) of cycles that intended to use surgically extracted sperm had no sperm available. Similarly, 12.5% (16/128) of cycles that created embryos with partner sperm ultimately had no embryo to transfer due to poor embryo development and aneuploidy. This was particularly pronounced in those with karyotypic abnormalities. This highlights the importance of preprocedure counseling. Couples should be prepared to proceed with either backup donor sperm or oocyte cryopreservation if inadequate sperm is found, and couples should be aware that severe male factor may affect embryo quality given that 16 cycles resulted in no embryo to transfer even when partner sperm was available. It is notable that of the 12 cycles in which partner sperm was not available, 4 were completely cancelled, 3 ultimately fertilized oocytes with partner sperm after oocyte cryopreservation, and 4 used donor sperm either immediately or after oocyte cryopreservation. The twelfth patient still has oocytes cryopreserved.

In a large population of azoospermic and severely oligospermic men whose female partners underwent IVF, the prevalence of karyotypic abnormalities was approximately 6.0% (67/1118), which is similar to previous reports. Our study, which is nearly four times larger than prior studies, found YCMs in only 4.4% (37/849) of our population, indicating that these genetic defects may be less common in men with azoospermia and severe oligospermia in the modern IVF patient population than previously reported. However, we should consider the nonexistence of results positive for AZFa and AZFb microdeletions in this cohort of couples undergoing IVF. Although our inclusion criteria allowed for the detection of men with AZFa or AZFb microdeletions if the female partner ultimately underwent IVF, no male partners were found to have AZFa or AZFb microdeletions. It is likely that none were present in this population of couples undergoing IVF, as it is generally understood that even after microdissection, sperm suitable for IVF/ICSI is extremely unlikely to be obtained (8, 14). Such couples were likely counseled to proceed with alternative options such as TDI, adoption, or childless living and would not have been captured in this population of couples undergoing IVF. In addition, a large study of nearly 5,000 infertile men with AZF deletions found that AZFc deletions are much more frequent compared with AZFa or AZFb. In this particular study, 60% of the deletions were AZFc, while 16% were AZFb, 5% were AZFa, and 14% were combinations (19). Thus, it is also possible that the relative infrequency of these deletions contributed to their absence.

Our study's main strength is the large sample size and the reliable diagnosis of "male infertility" on which the initial query was based. Additionally, we provide a more comprehensive assessment of IVF-ICSI outcomes in this patient population than previously published papers.

However, this descriptive study is not without limitations. The main limitation is that this cohort is limited to couples attempting IVF-ICSI and, thus, does not represent the full breadth of couples initially presenting with infertility who forgo treatment or attempt conception using TDI. While female infertility diagnoses were evaluated, we are unable to determine to what extent the coexistence of female factor infertility affects the outcomes examined. However, given that 75% of the cohort had a single diagnosis of male infertility, the relatively high LBR/OPR in those who had transfers, and the young female age in those who had no embryo to transfer, female factor infertility was likely a small contributor.

Although we present the data for cycles that used donor sperm for embryo creation, direct comparisons cannot be made. Some patients may have previously failed cycles with partner sperm before turning to donor sperm and may have a poorer prognosis. Similarly, our dataset only includes couples who were treated with IVF-ICSI, and those who were only treated with TDI were not captured in our query.

CONCLUSION

In patients with genetic causes of male factor infertility, it is reasonable to attempt the use of partner sperm. However, couples should be counseled regarding the possibility of having no sperm available, poor/failed fertilization, or no embryo(s) suitable for transfer. The specific outcome data provided by this analysis can be used to better counsel couples in whom the male partner has a karyotypic abnormality or YCM.

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