CASE REPORT

Severe systemic candidiasis following immunomodulation therapy in in vitro fertilisation-embryo transfer (IVF-ET)

Folasade Akhanoba, Jane MacDougall, Raj Mathur, Wassim Hassan

Department of Obstetrics and Gynaecology, Addenbrooke's Hospital, Cambridge, UK

Correspondence to
Dr Folasade Akhanoba,
sadez84@hotmail.com

Accepted 5 March 2014

SUMMARY

A 41-year-old nulliparous woman, with a medical history of unexplained infertility and multiple in vitro fertilisation (IVF) cycles with immunosuppressive therapy, was admitted to our tertiary obstetrics unit with sepsis at 18 weeks of pregnancy with dichorionic diamniotic twins. *Candida glabrata* was grown from her blood cultures, then subsequently from the liquor and placenta. She was treated with intravenous amphotericin, but unfortunately, the infection resulted in the rupture of her membranes, preterm labour and the demise of her twins. She delivered both twins at 23 weeks, 3 days apart. The antifungal agent was changed to high-dose fluconazole after delivery for 2 weeks and she is now well. Women undergoing IVF-embryo transfer with immunomodulation therapy have a potential risk of developing candidal chorioamnionitis and sepsis.

BACKGROUND

Candidaemia is rare in healthy, young individuals, although candidiasis is common. Pregnancy represents a risk factor for the occurrence of vulvovaginal candidiasis, and *Candida albicans* is usually the main culprit.^{1 2} There has been an increasing number of case reports of *Candida glabrata* infection associated with assisted fertility therapies.^{3–6} *C glabrata* is considered to be of low pathogenicity in individuals who are not immunocompromised. It is believed by some that the use of immunomodulation therapy in women with multiple failed in vitro fertilisation (IVF) cycles suppresses the immune system and reduces the risk of implantation failure. There is, however, no clear evidence that immunosuppression increases pregnancy rates after IVF.^{7 8} It is important to highlight the increased risks associated with its non-evidence-based use (ie, candidal sepsis) which can have detrimental effects on the woman and her pregnancy.

CASE PRESENTATION

A 41-year-old nulliparous community nurse with an 18-weeks gestation dichorionic diamniotic twin pregnancy following IVF was admitted to our tertiary obstetrics unit with a fever of unknown origin. She had a medical history of unexplained infertility and had completed eight cycles of IVF. As part of the last three cycles, she had been given immunosuppressive therapy. She had received infusions of tumour necrosis factor (TNF) inhibitor (monoclonal antibody adalimumab) in August 2011

and corticosteroids (prednisolone) in October 2011, February 2012 and April 2012. She also received lipid emulsion (intralipid) during this time. The latter course of corticosteroids was slowly decreased over 3 weeks.

She initially presented to us on 10 August 2012 with vaginal spotting. Vaginal examination revealed a long, closed cervix; the high vaginal swab taken at the time showed a heavy growth of *Candida* species. She re-presented on two more occasions with persistent vaginal spotting, and on her last presentation, which triggered her admission, she also reported abdominal and back pain, urinary frequency, general malaise and anorexia with chills and rigours. She was not feverish with a temperature of 37.2°C at the time of admission on 14 August 2012, but was started on co-amoxiclav for a presumptive urinary tract infection. During her hospital stay, her temperature started spiking above 38°C and her inflammatory markers were raised with a mild neutrophilia of $9.9 \times 10^9/L$ (reference $<7.7 \times 10^9/L$) and a C reactive protein (CRP) of 103 mg/L (reference <3.1 mg/L). Her antibiotic was changed from oral co-amoxiclav to intravenous ceftriaxone. Blood culture sets taken on days 2 and 3 of her admission were positive for *C glabrata*. Following consultation with the infectious diseases department, she was started on intravenous amphotericin (amphotericin). Ceftriaxone was continued. In view of the risk of endocarditis, endophthalmitis, hepatosplenic deposits and joint problems with candidaemia, various investigations were performed to rule these complications out. An echocardiogram and ophthalmoscopy were normal. Abdominal ultrasound demonstrated an enlarged spleen of 14 cm with no other abnormality. Routine anomaly ultrasound scan on 19 August was normal. On the sixth day of her admission, her alanine transaminase was noted to be deranged at 155 U/L (reference <40 U/L), so ceftriaxone was stopped. Her liver function tests gradually improved and normalised by 31 August (day 18).

Her membranes ruptured on the eighth day of her admission. She was started on erythromycin 250 mg four times a day as per local protocol, and a repeat ultrasound scan on 22 August revealed anhydramnios and reduced fetal movements of the first twin. The second twin had normal movements and amniotic fluid index. Culture of the liquor was positive for *Candida* species. Her clinical situation, however, continued to improve with no further fever.

CrossMark

To cite: Akhanoba F, MacDougall J, Mathur R, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-203202

Our colleagues from infectious diseases recommended that the amphotericin therapy should be continued intravenously for the duration of the pregnancy. The only suitable oral antifungal agent was fluconazole, which is linked to possible teratogenicity at high dose. A peripherally inserted central catheter (PICC line) was therefore placed. After 25 days of inpatient stay, on 7 September, she was discharged with arrangements for outpatient administration of amphotericin through her PICC line and weekly follow-up by our fetal medicine and infectious diseases departments.

Three days after her discharge, she was readmitted with abdominal pain at 22 weeks and 5 days gestation. An ultrasound scan demonstrated no fetal heart beat in the first twin, and anhydramnios and reduced fetal movements in the second twin. There were no clinical signs of sepsis, and her inflammatory markers remained stable with a neutrophil count of $10.5 \times 10^9/L$ (reference $<7.7 \times 10^9/L$) and a CRP of 30 mg/L (reference <3.1 mg/L). After long discussions with the couple, it was concluded that they would await events. She went on to deliver the first twin 2 days after, on 12 September at 14:40. Intermittent auscultation was performed on the second twin, with the plan that if no fetal heart beat was found, synthetic oxytocin could be started to induce the delivery of the second twin. On 15 September, after a heavy per vaginal bleed, the cervix was found to be dilated at speculum examination. A diagnosis of inevitable miscarriage was made, synthetic oxytocin was started and the second twin was delivered without any signs of life on the same day at 11:56. She required a manual removal of placenta in theatre. The placental cultures were positive for *C glabrata* and also *Streptococcus anginosus*. The latter organism was unexpected. Chromosomal analysis of the placenta did not demonstrate any evidence of trisomy.

OUTCOME AND FOLLOW-UP

The patient was discharged on a 2-week course of 800 mg oral fluconazole daily. Six weeks after her discharge, she was reviewed by the infectious diseases and fetal medicine teams in the postnatal counselling clinic, and was well. A high vaginal swab was repeated which was negative for *C glabrata* species and *S anginosus*.

She has since had an uneventful pregnancy, without any immunosuppressive therapy, after the transfer of two of her stored day six frozen embryos on 7 March 2013. High vaginal swabs were taken at 10, 18 and 32 weeks gestation, and they were all normal. Her son was delivered by elective caesarean section at 38 weeks and 6 days gestation on 15 November 2013. Mother and baby are doing very well.

DISCUSSION

C glabrata was initially known as *Torulopsis glabrata* before the genus *Candida* was named. It differs from other *Candida* species because it is monomorphic, non-pseudohypha forming, and it has a haploid genome.⁹ *C glabrata* is the second most frequently occurring fungus¹⁰ and the main non-albicans species that causes *Candida* vulvovaginitis. Pregnancy represents a risk factor for the occurrence of vulvovaginal candidiasis. The prevalence of *C glabrata* during pregnancy ranges from 2% to 8%,^{11 12} compared with 5–30% for *C albicans*.^{1 2} Despite the high prevalence of vaginal *Candida* colonisation during pregnancy, ascending infection leading to chorioamnionitis and candidaemia is still rare. *C glabrata*'s lack of pseudohypha formation results in decreased tissue adherence and difficulty in invading intact membranes⁹; hence many of its associated risk factors are those which permit direct introduction of the fungus

into the endometrial cavity. Predisposing risk factors include antibiotic therapy, immunosuppression, underlying medical conditions, such as diabetes mellitus, coexisting intrauterine device, IVF-embryo transfer (ET), cervical stitch, rupture of membranes, and amniocentesis or chorionic villous sampling.^{3 4 13} A review of 16 cases of *C glabrata* chorioamnionitis in 2012 revealed that 63% of the cases were associated with IVF, and 81% with some form of instrumentation.³ In 1997, Sfameni *et al*⁵ first demonstrated the importance of *C glabrata* vaginal colonisation in patients undergoing IVF, and the potential complication of introducing the fungus into the uterus at the time of ET. It has subsequently been suggested that a high vaginal swab should be performed and treatment initiated with boric acid or nystatin in women with positive culture results prior to ET.^{5 6}

Our patient had multiple risk factors. She had immunosuppressive therapy with her IVF-ET and the high vaginal swab from her first presentation revealed vaginal *Candida* colonisation, although the species was not identified until later. As she was not documented to have had a vaginal swab prior to her IVF cycles, we cannot be certain about the timing of the *Candida* colonisation. It would however be fair to speculate that this could have been as a result of her being immunosuppressed. The immunosuppression no doubt had a role to play in her development of candidaemia, a rare phenomenon. We can further speculate that the *C glabrata* was introduced into the uterine cavity at the time of the ET, proliferated and produced chorioamnionitis, which then led to the preterm rupture of membranes, preterm labour and demise of her twins. On the other hand, the *C glabrata* could have been introduced after she ruptured her membranes. The antibiotic therapy administered on her first admission would also have exacerbated her *Candida* infection. The indiscriminate empirical use of antibiotics is an unproven and possibly dangerous practice.

The major success rate limiting step in IVF is the implantation of the embryo after transfer. An imbalance in the secretion of T-helper 1 (Th1) and Th2 cytokines by natural killer cells, leading to a relative excess of Th1 (such as TNF- α) may be destructive to the trophoblast and endometrial cells, and lead to implantation failure.^{14 15} This is thought to precipitate autoimmune disease in susceptible individuals and has been linked to infertility. For this reason, therapies that help suppress natural killer cell activity and inhibit the cellular immune response (such as anti-TNF- α drugs and steroids) have been proposed as a safe and effective way of reducing the risk of implantation failure.¹⁶ However, studies have shown that short-term immunosuppression using corticosteroid does not make a statistically significant impact on the pregnancy rates in IVF-ET patients.^{7 8 17} Although a study by Taniguchi¹⁸ in 2005 concluded that implantation and clinical pregnancy rates were improved with corticosteroids, even in that study, the intervention had no effect on live birth rates. A recent study by Ying *et al*¹⁹ in China suggested that anticardiolipin antibody positive patients have a better IVF outcome if they are given methylprednisolone for immunosuppression and low-dose aspirin as an antithrombotic agent. They, however, did not specify how much of this positive effect is attributable solely to the immunosuppression.

Unfortunately, adverse effects are poorly and inconsistently reported.¹⁷ With the increased use of immunomodulation therapies in the care of fertility patients, there will be an increased risk of opportunistic fungal infections with potentially disastrous sequelae, as was seen in our patient. The difficulty in treating *C glabrata* infections is related to its reduced susceptibility to antifungal agents, such as azoles.⁹ Amphotericin B is the gold

standard for the treatment of systemic candidal infection until culture sensitivities are available. This is the case despite its adverse effects, namely maternal and neonatal deranged renal function and maternal hypokalaemia.²⁰ Fluconazole is better tolerated but we have limited data on its safety during pregnancy. Some case reports have suggested an increased risk of craniofacial abnormalities in the newborn,²¹ but this tends to be associated with high doses and prolonged periods of use. A Danish population-based cohort study did not demonstrate an increased risk of congenital malformations after exposure to a short course of fluconazole in early pregnancy.²²

The ethical use of unproven therapies in elective medicine, such as immunomodulation in assisted reproductive therapy (ART), remains controversial. The idea of patient autonomy and informed consent is the foundation for the ethical framework when applying these therapies. However, the paucity of evidence to support these therapies and the potential for physician and patient bias result in scepticism as to whether the consent is truly 'informed'. It is, therefore, important that physicians realise that informed consent only does not clear them of their responsibilities; they are also accountable for risk management.²³

Patient's perspective

Thank you for taking the time to write the case report. I do feel it is important for women undergoing IVF with immunomodulation to be fully informed of possible complications such as candidaemia, as highlighted in the learning points.

Learning points

- ▶ Women undergoing in vitro fertilisation (IVF) with immunomodulation should be informed of the potential complication of candidaemia, and should be offered screening at different intervals and treated as appropriate.
- ▶ Where immunosuppression therapy is used during IVF, we make the case for screening at different intervals in pregnancy with treatment as appropriate.
- ▶ In view of the paucity of evidence to support immunosuppression in patients undergoing IVF-embryo transfer, and the potential complications as demonstrated by this case, it is possible that the potential risks of (immune suppression) therapy outweigh any benefits. This also applies to the indiscriminate use of antibiotics.

Acknowledgements The authors would like to thank Mr Jeremy Brockelsby, Consultant in Obstetrics and Fetal Maternal Medicine at Addenbrooke's Hospital in Cambridge.

Contributors All authors contributed to the drafting and revision of the manuscript, and approved the final version.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Joseph PB, John PE, Howard WK, *et al.* Candida chorioamnionitis diagnosed by amniocentesis with subsequent fetal infection. *Rev Argent Microbiol* 2006;38:9–12.
- 2 Potasman I, Leibovitz Z, Sharf M. Candida sepsis in pregnancy and the postpartum period. *Rev Infect Dis* 1991;13:146–9.
- 3 Jackel D, Lai K. Candida glabrata sepsis associated with chorioamnionitis in an in vitro fertilisation pregnancy: case report and review. *Clin Infect Dis* 2013;56:555–8.
- 4 Ibara AS, Marcotelles P, Le Martelot MT, *et al.* Two cases of systemic Candida glabrata infection following in vitro fertilisation and embryo transfer. *Eur J Clin Microbiol Infect Dis* 2004;23:53–6.
- 5 Sfameni SF, Talbot JM, Chow SLS, *et al.* Candida glabrata chorioamnionitis following in vitro fertilisation and embryo transfer. *Aust N Z J Obstet Gynaecol* 1997;37:88–91.
- 6 Obegi A, Asemota MD, Nyirjesy P, *et al.* Candida glabrata complicating in vitro pregnancy: successful management of subsequent pregnancy. *Fertil Steril* 2011;95:803.e1–2.
- 7 Lee KA, Koo JJ, Yoon TK, *et al.* Immunosuppression by corticosteroid has no effect on the pregnancy rate in routine in-vitro fertilization/embryo transfer patients. *Hum Reprod* 1994;9:1832–5.
- 8 Mottla GL, Smotrich DB, Gindoff PR, *et al.* Increasing clinical pregnancy rates after IVF/ET. Can immunosuppression help? *J Reprod Med* 1996;41:889–91.
- 9 Fidel PL Jr, Vazquez JA, Sobel JD. Candida glabrata: review of epidemiology, pathogenesis, and clinical disease with comparison to *C. albicans*. *Clin Microbiol Rev* 1999;12:80–96.
- 10 Kalkanci A, Güzel AB, Khalil II, *et al.* Yeast vaginitis during pregnancy: susceptibility testing of 13 antifungal drugs and boric acid and the detection of four virulence factors. *Med Mycol* 2012;50:585–93.
- 11 Wenjin Q, Yifu S. Epidemiological study on vaginal Candida glabrata isolated from pregnant women. *Scand J Infect Dis* 2006;38:49–54.
- 12 Babic M, Hukic M. Candida albicans and non-albicans species as etiological agent of vaginitis in pregnant and non-pregnant women. *Bosn J Basic Med Sci* 2010;10:89–97.
- 13 Meizoso T, Rivera T, Fernandez-Acenero MJ, *et al.* Intrauterine candidiasis: report of four cases. *Arch Gynecol Obstet* 2008;278:173–6.
- 14 Krishnan L, Guilbert LJ, Wegmann TG, *et al.* T helper 1 response against Leishmania major in pregnant C57BL/6 mice increases implantation failure and fetal resorption: correlation with increased IFN-gamma and TNF and reduced IL-10 production by placental cells. *J Immunol* 1996;156:653–62.
- 15 Thum MY, Bhaskaran S, Abdalla HI, *et al.* An increase in the absolute count of CD56dimCD16+CD69+ NK cells in the peripheral blood is associated with a poorer IVF treatment and pregnancy outcome. *Hum Reprod* 2004;19:2395–400.
- 16 Winger EE, Reed JL, Ashoush S, *et al.* Treatment with adalimumab (humira) and intravenous immunoglobulin improves pregnancy rates in women undergoing IVF. *Am J Reprod Immunol* 2009;61:113–20.
- 17 Boomsma CM, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. *Cochrane Database Syst Rev* 2012;6. doi:10.1002/14651858.CD005996.pub3.
- 18 Taniguchi F. Results of prednisolone given to improve the outcome of in vitro fertilisation-embryo transfer in women with antinuclear antibodies. *J Reprod Med* 2005;50:383–8.
- 19 Ying Y, Zhong YP, Zhou CQ, *et al.* A retrospective study of IVF outcome in patients with anticardiolipin antibody: effect of methylprednisolone plus low-dose aspirin adjuvant treatment. *J Reprod Immunol* 2012;94:196–201.
- 20 Dean JL, Wolf JE, Ranzini AC, *et al.* Use of amphotericin B during pregnancy: case report and review. *Clin Infect Dis* 1994;18:364–8.
- 21 Pursley TJ, Blomquist IK, Abraham J, *et al.* Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis* 1996;22:336–40.
- 22 Norgaard M, Pedersen L, Gislum M, *et al.* Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother* 2008;62:172–6.
- 23 Al Eydhy A, Razack S. The ethics of using innovative therapies in the care of children. *Paediatr Child Health* 2008;13:181–4.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow