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Original Article

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Cryptococcosis in pregnancy and the postpartum period: Case series and systematic review with recommendations for management

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Abstract

Cryptococcal meningitis causes 15% of AIDS-related deaths. Optimal management and clinical outcomes of pregnant women with cryptococcosis are limited to case reports, as pregnant women are often excluded from research. Amongst pregnant women with asymptomatic cryptococcosis, no treatment guidelines exist. We prospectively identified HIV-infected women who were pregnant or recently pregnant with cryptococcosis, screened during a series of meningitis research studies in Uganda from 2012 to 2018. Among 571 women screened for cryptococcosis, 13 were pregnant, one was breastfeeding, three were within 14 days postpartum, and two had recently miscarried. Of these 19 women (3.3%), 12 had cryptococcal meningitis, six had cryptococcal antigenemia, and one had a history of cryptococcal meningitis and was receiving secondary prophylaxis. All women with meningitis received amphotericin B deoxycholate (0.7–1.0 mg/kg). Five were exposed to 200–800 mg fluconazole during pregnancy. Of these five, three delivered healthy babies with no gross physical abnormalities at birth, one succumbed to meningitis, and one outcome was unknown. Maternal meningitis survival rate at hospital discharge was 75% (9/12), and neonatal/fetal survival rate was 44% (4/9) for those mothers who survived. Miscarriages and stillbirths were common ($n = 4$). Of six women with cryptococcal antigenemia, two received fluconazole, one received weekly amphotericin B, and three had unknown treatment courses. All women with antigenemia survived, and none developed clinical meningitis. We report good maternal outcomes but poor fetal outcomes for cryptococcal meningitis using amphotericin B, without fluconazole in the first trimester, and weekly amphotericin B in place of fluconazole for cryptococcal antigenemia.

Key words: *Cryptococcus*, pregnancy, HIV/AIDS, antifungal agents, systematic review.

Introduction

Human immunodeficiency virus (HIV) is the leading cause of death worldwide for women of childbearing years.[1] While antenatal care and prevention of mother-to-child transmission (PMTCT) programs have rapidly scaled up services in sub-Saharan Africa, there remain gaps in the cascade of care for women with HIV infection.[2–4] Globally, there were 800,000 new HIV infections among women in 2017.[5] Lack of access to care, suboptimal antiretroviral therapy (ART) adherence, and high rates of loss to follow-up can put HIV-infected

pregnant women at an increased risk for opportunistic infections, such as cryptococcosis.[6]

Globally, *Cryptococcus* causes 15% of AIDS-related mortality with an estimated 70% mortality in sub-Saharan Africa in routine care.[7] Women of childbearing age comprise approximately 41–55% of cryptococcal patients in Africa[8–11]; however, the incidence of cryptococcosis in HIV-infected pregnant women is unknown.[12,13] Pregnant women are largely excluded from clinical mycology research due to fluconazole teratogenicity, a critical antifungal agent used in cryptococcal treatment. Knowledge of cryptococcosis and pregnancy is therefore strictly limited to a few published case reports.

Treatment guidelines related to cryptococcosis in pregnancy are subsequently based on expert opinion. For nonpregnant persons with symptomatic cryptococcal meningitis, recommended treatment includes amphotericin B (0.7–1.0 mg/kg) and flucytosine.[14] As flucytosine is unavailable in low- and middle-income countries where the burden of cryptococcosis is highest, the combination of amphotericin B and high dose fluconazole (1200 mg daily) is used.[15] While amphotericin B can be given in pregnancy (FDA Category B), high dose fluconazole is teratogenic and should be avoided in the first trimester.[14,16] This risk is thought to decrease in later trimesters, but limited clinical data exist regarding the safety of prolonged high-dose fluconazole during pregnancy. Providers must therefore weigh uncertain fetal risks with known maternal benefits in deciding whether to initiate fluconazole in the later trimesters or wait until the postpartum period. Following meningitis treatment, daily fluconazole is recommended as secondary prophylaxis for 1 year until $CD4^+$ counts reaches >200 cells/μl or >100 cells/μl with HIV viral suppression. For pregnant women or women who become pregnant while on fluconazole secondary prophylaxis, no recommendations exist.

Similarly, there are no treatment guidelines for pregnant women who are serum cryptococcal antigen positive (CrAg+) and at a high risk for meningitis and death.[17,18] The World Health Organization (WHO) recommends universal screening for cryptococcal antigen (CrAg) in HIV-infected persons with $CD4^+$ counts <100 cells/μl, followed by high dose fluconazole preemptive therapy for those CrAg+ without meningitis.[14,15] This CrAg screening and preemptive treatment approach reduces the risk of meningitis and death, though there are presently no CrAg screening studies that include pregnant women.[19]

In summary, treatment of any stage of cryptococcal infection according to international guidelines often requires high doses of a teratogenic antifungal medication, presenting a difficult clinical dilemma during pregnancy. Herein we present the largest case series to date of HIV-infected pregnant women with cryptococcosis and summarize the medical literature of HIV-related cryptococcosis in pregnancy, providing our suggestions for clinical management.

Methods

Case series

From 2012 to 2018, we conducted a series of prospective clinical trials and cohort studies in Kampala and Mbarara, Uganda, for HIV-infected adults with cryptococcal infection. Institutional Review Board and other regulatory approvals occurred through the Joint Clinical Research Centre (JCRC), Mulago National Referral Hospital in Uganda, and the University of Minnesota.

Two studies enrolled asymptomatic persons with cryptococcal antigenemia without central nervous system (CNS) disease (NCT03002012, NCT01535469), and one combination phase II then phase III clinical trial enrolled persons with cryptococcal meningitis (NCT01802385).[20,21] The two asymptomatic cryptococcal antigenemia clinical trials CrAg screened asymptomatic, HIV-infected participants with $CD4^+$ count <100 cells/μl from outpatient clinics throughout Uganda. The meningitis clinical trial screened any participant with suspected meningitis, where a positive cerebrospinal fluid (CSF) cryptococcal antigen assay (LFA, Immy, Norman, OK, USA) and CSF culture confirmed *Cryptococcus neoformans* infection.

All women who were screened fingerstick/serum CrAg+ had a urine and/or serum human chorionic gonadotropin (hCG) test to document pregnancy status. Women who were pregnant were excluded from the three interventional studies. However, written informed consent was obtained prior to screening for suspected meningitis, where participants consented for the collection of clinical outcomes despite exclusion from interventional studies.

In the Results section, three illustrative cases of management of cryptococcal infection in pregnancy are described to further elucidate the complexity of clinical management in this patient population.

Literature review

A literature search was conducted to investigate additional cases of HIV-related cryptococcosis in pregnancy. We searched PubMed/MEDLINE using a combination of the MeSH keywords "cryptococcosis," "cryptococcal meningitis," "pregnancy," "postpartum," "AIDS," and "HIV," for English language publications from 1950 to present day (July 30, 2018). The first author reviewed the potential publications and references for relevance. Studies unrelated to HIV-infected pregnant persons with cryptococcosis were excluded. A second manual search was then conducted to identify any missing articles that were not captured under the above MeSH terms.

A second literature search was performed to identify additional clinical trials that reported screened cases of pregnant or breastfeeding women with cryptococcosis who were excluded from clinical research. A PubMed/MEDLINE search was conducted using the keyword "cryptococcal meningitis," and the search was limited to clinical trials. The first author reviewed

publications for relevance and scanned publications for mention of identified pregnant and/or breastfeeding screened participants.

Results

Case series

From 2012 to 2018, there were 571 women screened with cryptococcal infection in Uganda. Four hundred and seventy-eight of these participants had cryptococcal meningitis, and 93 had asymptomatic cryptococcal antigenemia. Of these 571 cases, 18 women were pregnant/recently postpartum at time of cryptococcal disease screening. One additional woman became pregnant following cryptococcal meningitis treatment while receiving secondary prophylaxis. A total of 19 cases (3.3%) of cryptococcal disease in pregnancy/the postpartum period were therefore subsequently identified.

Cryptococcal meningitis

During 2012–2018, 1767 Ugandans presented with suspected meningitis, and 1174 (66%) had confirmed cryptococcal meningitis. Of these, 478 (41%) cryptococcal meningitis cases occurred in women. Eleven (2.3%) of these women were pregnant or recently pregnant (within 14 days) at diagnosis. In addition to these 11 women, there was one additional pregnant woman with cryptococcal meningitis identified through outpatient CrAg screening and one reported case of ectopic pregnancy while on 200 mg daily fluconazole maintenance therapy following induction and consolidation therapies several months prior. This woman discovered she was two months pregnant before discontinuing fluconazole. See Table 1.

Of the 12 hospitalized pregnant women with cryptococcal meningitis, two presented during the first trimester and five during the second trimester of pregnancy; two presented during or shortly after miscarriage, and three presented 1–2 weeks postpartum. The median duration of meningeal symptoms prior to diagnosis was 14 days. The mean age was 28 years (range 18–35), and median $CD4^+$ count was 19 cells/μl (interquartile range [IQR] 8–36). Five women were ART-naive, six were ART-experienced, and one had defaulted from HIV care. ART was initiated 1–4 months prior to meningitis diagnosis among five of the six ART-experienced women, none of whom received pre-ART CrAg screening. Nine of the 12 women (75%) survived through initial hospitalization (95% confidence interval [CI]: 43–95%). Of these nine women, four delivered healthy infants (44%), three miscarried (33%), one had a stillbirth (11%), and one (11%) was lost to follow-up (Table 1).

All 12 women with cryptococcal meningitis received amphotericin B deoxycholate (0.7–1.0 mg/kg); five received additional weekly outpatient amphotericin B deoxycholate, substituting consolidation and maintenance fluconazole therapy (see Case 1). Five women were exposed to fluconazole at varying stages of pregnancy, including one woman in first trimester (see Case 2). No newborn congenital abnormalities were observed. In our cohort, four women experienced a miscarriage/stillbirth. None of these women were exposed to fluconazole during pregnancy.

Of the three women with postpartum cryptococcal meningitis, one received 14 doses of amphotericin B (0.7–1.0 mg/kg) and was subsequently treated for unmasking immune reconstitution inflammatory syndrome (IRIS) but died.[22] The second woman received amphotericin B and 800 mg/day fluconazole but died on the second day. A newborn heel stick CrAg was negative. The third woman was diagnosed with cryptococcal meningitis 2 weeks postpartum and was exclusively breastfeeding. She received 14 days amphotericin B and 1200 mg fluconazole daily. A newborn heel stick CrAg was negative at 3 weeks.

Serum cryptococcal antigenemia

Of the 93 CrAg+ women screened from outpatient clinics using lab-based reflexive CrAg screening, five (5.4%) were pregnant or breastfeeding. Two additional pregnant women with cryptococcal antigenemia without CNS disease were identified through CrAg screening in the hospital. One of these seven pregnant women was symptomatic in her second trimester with serum CrAg titers 1:320 and CrAg+ cerebrospinal fluid (CSF) (Table 1). The other six CrAg+ pregnant women were either asymptomatic or CSF CrAg-negative at time of cryptococcal screening (Table 2). Of these six serum CrAg+ pregnant women, screening occurred during second trimester ($n = 1$), during the postpartum, breastfeeding period ($n = 1$) and at unknown stages of pregnancy ($n = 4$). Of those with recent $CD4^+$ counts, the median $CD4^+$ was 71 (IQR 61–95) cells/μl. Two of the mothers had CrAg serum titers drawn (1:20 and 1:5000). One woman was ART-naive, while the other five were ART-experienced.

Two of the six CrAg+ women received high dose fluconazole, one was treated with weekly amphotericin B (0.7–1.0 mg/kg) in place of fluconazole (see Case 3), and three had unknown treatment. All six CrAg+ women survived to hospital discharge, and of three with known 6-month outcomes, all survived without developing meningitis (Table 2).

Illustrative case reports

Case 1: Weekly amphotericin B in place of fluconazole consolidation after cryptococcal meningitis

A 32-year-old HIV-infected woman, who was ART-naive, presented to hospital with 21 days of headache and vomiting. $CD4^+$ was 33 cells/μl. The woman tested fingerstick CrAg+. CSF CrAg was positive, and CSF culture grew 141,000 *Cryptococcus* colony forming units (cfu)/ml. Urine hCG was positive and ultrasonography revealed a twin gestation around 16 weeks. The patient was treated with a 14-day course of amphotericin B

Table 1. Observed cases of HIV-related cryptococcal meningitis in pregnancy in Uganda from 2012 to 2018.

No.	Disease severity	Treatment*	Duration of symptoms (days)	EGA (weeks)	Age	Recent $CD4^+$ count (cells/μl)	ART status	Outcome of mother	Outcome of baby
1	430,000 cfu/ml in CSF	Amphotericin B: 14 doses, followed by 7 additional weekly outpatient doses Fluconazole: 800 mg for 9 days during 1st trimester, 200 mg fluconazole during 3rd trimester	14	6	18	7	ART defaulter	Alive	No abnormalities, alive; HIV-
2		Amphotericin B: 17 doses prior to screening at nearby facility, 14 doses after repeated high growth	4	N/A	23	34	ART experienced, (TDF/3TC/EFV), 10 weeks prior	Alive at discharge	Miscarriage day 1 into treatment
3	1100 cfu/ml in CSF (CSF CrAg titers 1:4000)	Amphotericin B: unknown number of doses Fluconazole: 800 mg for 3 days in 2nd trimester (EGA 14 weeks), 400 mg/day at hospital discharge (2nd trimester, EGA 16 weeks)	14	14	35	19	ART naive	Alive at discharge	Unknown
4	14,200 cfu/ml in CSF (CSF CrAg titers 1:700)	Amphotericin B: 14 doses, followed by weekly outpatient amphotericin B	14	7	24	7	ART naive	Alive at discharge	Miscarriage at ~12 weeks EGA, confirmed by ultrasound
5	141,000 cfu/ml in CSF	Amphotericin B: 14 doses, followed by weekly outpatient amphotericin Fluconazole: 200 mg/day 3rd trimester	21	16, twin gestation	32	33	ART naive	Alive	Twin babies without abnormalities, CrAg
6	320,000 cfu/ml in CSF	Amphotericin B: 14 doses Fluconazole: 800 mg/day post-miscarriage	4	N/A	21	7	ART naive	Alive at discharge	Miscarriage, few days before diagnosis
7		Amphotericin B: unknown number of doses Fluconazole: discharged on unknown dose of daily fluconazole	14	~24	35	40	ART experienced, (TDF/3TC/EFV), ~4 months	Alive	Delivered at term without abnormalities; CrAg, HIV status unknown
8		Amphotericin B: 6 doses prior to death Fluconazole: unknown dose prior to death	90	~20	32	13	ART naïve	Death six days into treatment	Death
9	Postpartum IRIS [22]	Amphotericin B: 14 doses	30	1 week postpartum	30	38	ART experienced, ~1 month	Death	Without abnormalities, CrAg-
10	Postpartum	Amphotericin B: 2 doses postpartum prior to death Fluconazole: 800 mg/day for two days prior to death	21	~3 days postpartum	29	9	ART experienced (TDF/3TC/EFV), ~3 months	Death two days into treatment after CM diagnosis	Premature, 2.1 kg, CrAg-, HIV- baby was delivered at 36 weeks before the mother's condition deteriorated
11	369,000 cfu/ml in CSF, postpartum	Amphotericin B: 14 doses Fluconazole: 1200 mg/day	14	2 weeks postpartum; exclusively breastfeeding	30	37	ART experienced (AZT/3TC/NVP), 2 years, HIV viral load 34,872 copies/ml	Alive at discharge	Started on ABC/3TC/ Aluvia for high-risk pregnancy, was CrAg- during first month of life

Table 1. (*Continued*).

No.	Disease severity	Treatment*	Duration of symptoms (days)	EGA (weeks)	Age	Recent $CD4^+$ count (cells/μl)	ART status	Outcome of mother	Outcome of baby
12	Post-CM receiving secondary prophylaxis	Fluconazole: Was on 200 mg/day maintenance therapy when found to be 2 months pregnant	N/A	8	27	208	ART experienced (TDF/3TC/EFV)	Alive	Ectopic pregnancy
13	Serum CrAg titer 1:320, on/off HA, but not overtly symptomatic, CSF CrAg+	Amphotericin B: 7 doses during hospitalization, 4 doses weekly outpatient prior to lost to follow-up	N/A	26	25	N/A	ART experienced (TDF/3TC/EFV), 1 month	Alive	Stillbirth

Abbreviations: CM, cryptococcal meningitis; EGA, estimated gestational age; HA, headache; N/A, not available.
*Amphotericin B = amphotericin B deoxycholate (0.7–1.0 mg/kg).

Table 2. Observed cases of HIV-related cryptococcal antigenemia in pregnancy in Uganda from 2012 to 2018.

No.	Disease severity	Treatment*	Duration of symptoms (days)	EGA (weeks)	Age	Recent $CD4^+$ count (cells/μL)	ART status	Outcome of mother	Outcome of baby
1	Asymptomatic	Fluconazole: 200 mg/day postpartum	N/A	Exclusively breastfeeding (8 months postpartum)	25	N/A	ART experienced (TDF/3TC/EFV), unknown duration	Alive at six months	Alive, CrAg- at 6 months
2	Asymptomatic (Serum CrAg titers 1:20)	Amphotericin B: 10 doses throughout pregnancy	N/A	24	34	N/A	ART experienced (TDF/3TC/EFV), unknown duration	Alive postpartum	Alive
3	Asymptomatic	Unknown	N/A	Unknown	27	73	ART experienced (TDF/3TC/NVP), 1 year	Alive at six months	Unknown
4	Asymptomatic (Serum CrAg titers 1:5000)	Unknown	N/A	Unknown	35	69	ART naive	Alive at six months	Unknown
5	Symptomatic (Fingerstick CrAg+, CSF CrAg-)	Unknown	10	Unknown	21	38	ART experienced, unknown regimen and duration	Alive at hospital discharge	Unknown
6	Symptomatic, CSF India ink + (History of CM)	Fluconazole: Was receiving 400 mg/day prior to CrAg screening	14	Unknown	29	160	ART experienced (AZT/3TC/EFV), 2 years	Alive at hospital discharge	Unknown

Abbreviations: CM, cryptococcal meningitis; EGA, estimated gestational age; N/A, not available. *Amphotericin B = amphotericin B deoxycholate (0.7–1.0 mg/kg).

deoxycholate without fluconazole. After 12 days of treatment, CSF quantitative cryptococcal culture grew 280 cfu/ml. She then received 12 additional weekly outpatient doses of amphotericin B in place of fluconazole consolidation therapy. The woman was started on first line ART therapy and was reportedly doing well at 32 weeks gestation. She declined most therapeutic lumbar punctures throughout her course of management but was started on 200 mg/day fluconazole at 18 weeks of treatment (EGA 34 weeks). The woman delivered two healthy HIV-negative infants who were heelstick CrAg-negative.

Case 2: Fluconazole in first trimester

An 18-year-old HIV-infected woman who had defaulted from ART care presented to hospital with 2 weeks of headaches, visual blurring, photophobia, and vomiting. GCS was 14 and $CD4^+$ was 7 cells/μl. Diagnostic lumbar puncture revealed raised CSF opening pressure of 490 mm H_2O. CSF CrAg was positive and CSF culture grew 430,000 *Cryptococcus* cfu/ml. Urine hCG was read as negative. The woman started 800 mg/day fluconazole and amphotericin B daily. Upon her 12th day of treatment, an abdominal ultrasound demonstrated an intrauterine pregnancy at approximately 6 weeks gestation. Fluconazole was immediately stopped, and the patient continued amphotericin B for a total of 14 days. CSF cultures at day 14 remained positive. She received seven additional weekly doses of outpatient amphotericin B and therapeutic lumbar punctures. The woman's CSF eventually sterilized by week 10 of treatment, and she was started on low dose fluconazole 200 mg daily during her second trimester (at EGA of 16 weeks). She delivered a healthy HIV-negative baby boy without any gross anomaly.

Case 3: Treatment of asymptomatic CrAg+ antigenemia in second trimester

A 34-year-old HIV-infected woman who was 24 weeks pregnant presented to an outpatient HIV clinic in Kampala, Uganda. She was ART-experienced and tested plasma CrAg+ with a CrAg LFA titer of 1:20, without signs or symptoms of cryptococcal meningitis. Instead of standard of care preemptive fluconazole therapy, she was treated with biweekly doses of amphotericin B deoxycholate 50 mg in the second trimester. She received a total of 10 doses of amphotericin B over 20 weeks and remained asymptomatic. She delivered a healthy full-term infant without congenital anomalies.

Literature review

In our literature search, we identified 11 cases of cryptococcal infection in HIV-infected pregnant and postpartum women (Supplemental Fig. 1). Of these, all had either cryptococcal meningitis or disseminated cryptococcal disease. Three women presented during second trimester, and eight presented during third trimester or the postpartum period. Five women were treated with fluconazole during pregnancy and two postpartum. See Table 3 for further details of treatment.[12,22–31] Six (55%) of the 11 women survived, four died postpartum, and one died following a miscarriage. Nine of the 11 women (82%) delivered newborns. No cases of asymptomatic cryptococcal antigenemia were reported in HIV-infected pregnant women.

We additionally identified the number of pregnant women screened in clinical trials for cryptococcosis that were excluded due to pregnancy. Using our search criteria, 108 articles were scanned for mention of pregnant and/or breastfeeding screened participants (Supplemental Fig. 2). Seven studies reported a combined total of 19 cases of HIV-associated cryptococcosis in pregnancy and/or the postpartum period. The prevalence of pregnant or breastfeeding women among participants with cryptococcosis screened for study eligibility was 0.60% (95% CI, 0.36 to 0.94%). All these women were excluded from the clinical research trials (Supplemental Table 1).[9-11,32-35]

Discussion

We present the largest case series to date of HIV-infected pregnant women with cryptococcosis. We identified 19 cases of cryptococcosis in HIV-infected pregnant/postpartum women with an overall prevalence of 3.2% (18/571), with one additional incident pregnancy. We also present the first cases of pregnant women with asymptomatic cryptococcal antigenemia.

In comparison to the 11 published cases of HIV-related cryptococcosis in pregnancy, our study population had a higher maternal meningitis survival rate (75% compared with 55% in the literature) but lower percentage of pregnancies carried to delivery (44% compared with 82% in the literature). Our observed survival rate may be related to more intensive clinical care in a research setting, however the 95% CI (43–95%) associated with survival was wide and therefore of unclear significance. Miscarriage and stillbirths were common in our patient population (none of whom had received fluconazole), similar to other HIV-infected cohorts, likely reflective of the severity of underlying disease.[36,37] While all reports in the literature described HIV-infected pregnant women with disseminated or CNS disease, approximately 32% of our cases were serum CrAg+ women without meningitis. This group of HIV-infected pregnant women with asymptomatic cryptococcal antigenemia is a unique population of interest where no current treatment guidelines exist.

In HIV-infected pregnant women, CrAg screening is paramount but may not always be adequately pursued. In our cohort, five women had recently initiated ART 1–4 months prior to meningitis diagnosis. While the test-and-treat approach to HIV care encourages early ART initiation, assessing $CD4^+$ counts remains important. Had these women been CrAg screened based upon their $CD4^+$ counts prior to or at ART initiation and treated for cryptococcal antigenemia, it is likely that the progression to

Table 3. Summary of known cases of HIV-related cryptococcosis in pregnancy and the postpartum period in the literature.

No.	Disease State	Serum CrAg titers	CSF CrAg titers or cultures	Treatment	EGA (weeks)	Age (years)	$CD4^+$ count (cells/μl)	Outcome of mother	Outcome of child	Reference
1	CM (Prior history of CM)	1:256	1:8	Initial: 14 days amphotericin B (1 mg/kg daily), no repeat LPs, no fluconazole Two weeks later (after recurrent symptoms): 14 additional days of amphotericin B, 400 mg/day fluconazole	16	20	3	Alive	Delivered at 37 weeks (C-section), placental cryptococcosis; HIV- at 1 year, no evidence of cryptococcosis	Nayak[12]
2	CM, post-partum: CM-IRIS	+	1:200	Pregnancy: IV fluconazole 800 mg/day x 30 days; Postpartum: amphotericin B 50 mg IV daily and oral fluconazole 400 mg 2x/day	29	32	67	Worsened mental status day 3+ postpartum, died on day +10	Delivered day +30 of treatment (vaginal), 1.9 kg, heel stick CrAg-, Apgar score 5 and 10	Kiggundu[22]
3	CM	1:4096	1:218	Amphotericin B, unknown dose / duration	28	19	20	Developed preeclampsia, survived CM, but died 12 months postpartum from sepsis	Delivered at 28 weeks (C-section), 1.1 kg, bilateral lung disease; placental cryptococcosis, HIV-, CrAg titer 1:2 on 5th day of life, CrAg- bronchoalveolar fluid	M Patel[23]
4	Postpartum unmasking CM	N/A	Culture positive	Amphotericin B, unknown dose / duration	33	26	N/A	Died 14 days postpartum	CM at 92 days of life (HIV-, born premature at 33 weeks, 1300 g, Apgar score 7 and 10)	Sirinavin[24]
5	Postpartum unmasking CM	N/A	Culture positive	Amphotericin B (4,075 mg) over 80 days; Fluconazole maintenance therapy	41	26	N/A	Died nine days after relapsing symptoms	Vaginal delivery, 2880 g, Apgar score of 9 and 10. Not breastfed, had cough/fever on day 52 of life, *Cryptococcus* found in blood, died day 54	Castro[25]
6	Postpartum unmasking CM	N/A	1:100 India Ink+	Initial: Amphotericin B 0.7 mg/kg for 21 days, IV methylprednisolone 1 gm IV x5 days, 400 mg/day fluconazole for 8 weeks	36	25	166	Alive	Stillborn	More[26]
7	CM (Prior history of CM)	+	+	14 days amphotericin B followed by fluconazole; at 34 weeks: restarted fluconazole due to non-adherence	17	20	3	Alive (later relapsed)	Delivered at 38 weeks (C-section), 2.9 kg, Apgar score 8 and 9, serum CrAg-, HIV-, placental cryptococcosis	Darko[27]
8	Genital tract *Cryptococcus*	N/A	N/A	None	3rd trimester	28	N/A	Death day 1	Miscarriage	Rahimi[28]
9	Disseminated *Cryptococcus*	+	N/A	Not reported	40	30	N/A	Death	Delivered at 40 weeks (C-section), 3.48 kg; Apgar score 9 and 9, placental cryptococcosis	Kida[29]
10	CM	N/A	Culture positive	Pregnancy: Two weeks amphotericin B, 800 mg/day and 400 mg/day fluconazole in 3rd trimester; Breastfeeding: 200 mg/day fluconazole	30	34	243	Alive	Delivered at 36 weeks, healthy, 1.8 kg baby boy without noticeable congenital abnormalities	Bright[30]
11	CM	+	Culture positive	Amphotericin B 50 mg daily + 800 mg/day fluconazole in 3rd trimester	29	31	379	Alive	Vaginal delivery at ~32 weeks, 2.1 kg, Apgar scores 7 and 9	Ngwenya[31]

Abbreviations: CM, cryptococcal meningitis; EGA,= estimated gestational age; N/A, not available.

Table 4. Suggested treatment of cryptococcal meningitis and cryptococcal antigenemia in pregnancy.

	Treatment in nonpregnant adults[15]	Suggested treatment in pregnant women[b]	Concerns in pregnancy
Induction[a]	Amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, 4 doses/day) for 1 week, followed by 1 week of fluconazole (1200 mg/day) OR Amphotericin B deoxycholate (1.0 mg/kg/day) and fluconazole (1200 mg daily) for 2 weeks	**1st trimester:** Amphotericin B deoxycholate (1.0 mg/kg/day) for 2 weeks **2nd/3rd trimester:** Amphotericin B deoxycholate (1.0 mg/kg/day) for 2 weeks	**Flucytosine:** Category C **Animal studies:** ○ Teratogenic in rats [46–47] **Human studies:** ○ 1st trimester: contraindicated [48] ○ 2nd/3rd trimester: no increased risk of congenital abnormalities [40, 48–55, 84] ○ Unknown if excreted in breast milk[46]
Consolidation	Fluconazole 800 mg/day, 8 weeks	**1st trimester:** Amphotericin B deoxycholate (1.0 mg/kg/day) every week until 2nd trimester **2nd/3rd trimester:** 400 mg/day fluconazole for 8 weeks	**Fluconazole:** Category C: low dose (one time 150 mg), Category D: high dose (>150 mg) [55] **Animal studies:** ○ Teratogenic in animals [56–59] ○ Peak risk at equivalent of ~4 weeks during neural crest development with risk through humans ~12 weeks.
Maintenance Secondary Prophylaxis	Fluconazole 200 mg/day for 1 year until $CD4^+$ reaches >100 cells/mm^3 and virologically suppressed. If viral load is not available, continue fluconazole for 1 year until $CD4^+$ reaches >200 cells/mm^3	**1st trimester:** **If $CD4^+$ <100:** weekly Amphotericin B deoxycholate (1.0 mg/kg/day) until 2nd trimester **If $CD4^+$ 100–200 and viral load >1000 copies:** weekly Amphotericin B deoxycholate (1.0 mg/kg/day) until 2nd trimester **If $CD4^+$ 100–200 and viral load <1000:** stop fluconazole **2nd/3rd trimester:** **If $CD4^+$ <200:** fluconazole 200 mg/day **If $CD4^+$ >200:** stop fluconazole	**Human studies:** **High dose (400 mg/day or above):** ○ Congenital abnormalities potentially related to fluconazole [60–63] ○ No reported/known congenital abnormalities [12, 22, 30–31, 40, 51, 64–69] **Low dose (150–200 mg):** ○ Congenital abnormalities potentially related to fluconazole [70] ○ No reported/known congenital abnormalities [66–67, 71–78] ○ No increased incidence of stillbirth. Increased hazard ratio, but no increased incidence of miscarriage [79]
Antigenemia	Fluconazole 800 mg/day, 2 weeks Fluconazole 400 mg/day, 8 weeks Fluconazole 200 mg/day, 6 months; stop thereafter	**1st trimester:** Amphotericin B deoxycholate (1.0 mg/kg/day) weekly until 2nd trimester if CrAg titer ≥1:160. If CrAg titer 1:40 to 1:80, fluconazole 200 mg/day, with close monitoring. If CrAg titer ≤1:20 close monitoring until 2nd trimester. Repeat CrAg titer **2nd/3rd trimester:** Amphotericin B deoxycholate weekly for 2 weeks, 400 mg/day fluconazole for 10 weeks, stop	

[a]Liposomal amphotericin B may be a preferable alternative to amphotericin B deoxycholate if available.

[b]**For postpartum/breastfeeding women and women of childbearing age:** treat as nonpregnant patients and monitor infant for toxicity.[80–83] Counsel women regarding risk of fluconazole teratogenicity should she become pregnant and discuss family planning. Stop fluconazole at 1 year and recheck $CD4^+$ count. If $CD4^+$ >100 and virologically suppressed, stop fluconazole.

meningitis (and death for two women) would have been prevented. In areas where $CD4^+$ testing is unavailable, universal CrAg screening in the setting of new HIV diagnoses and in those with virologic failure may be beneficial.[38] Since HIV-infected pregnant women may be at a higher risk of cryptococcal-related morbidity, mortality, or IRIS than other patients due to the immunologic changes and reduction in T helper type 1 (Th1) $CD4^+$ cells that naturally occurs with pregnancy, identification and proper treatment is critical.[39,40] Cases of placental cryptococcosis[12,23,27,29,41] and vertical transmission of cryptococcosis

have been documented in the literature[23,24]; further necessitating CrAg screening amongst HIV-infected pregnant women and newborns of women with cryptococcosis.

In our population of pregnant women with cryptococcal antigenemia but without meningitis, we observed treatment success using weekly amphotericin B in place of preemptive fluconazole therapy. Weekly amphotericin B is used in other populations as prophylaxis for various mycoses.[42,43] While it is inferior to fluconazole in preventing cryptococcal relapse, it is safe in pregnancy unlike fluconazole.[44,45] Flucytosine, another potential antifungal therapy, is teratogenic in rats, but no human studies have been performed.[46,47] In our cohort of pregnant women with cryptococcal meningitis, five women received fluconazole in addition to amphotericin B. While we did not find any congenital abnormalities in these women, fluconazole is a known teratogen in first trimester and should be avoided if possible. The risk of teratogenicity should ultimately be considered against the risk of maternal death, as cryptococcal meningitis is fatal in ~70% of cases in sub-Saharan Africa.[7] Table 4 presents our approach to cryptococcosis during pregnancy, considering the risk of fluconazole teratogenicity, gestational age, HIV viral load, $CD4^+$ cell count, and blood CrAg titer.[12,15,22,30,31,40,46–84]

Following cryptococcal meningitis treatment, providers should inform women of childbearing age of the risk of fluconazole teratogenicity should they become pregnant while receiving antifungal maintenance therapy. Nonpregnant patients recovering from cryptococcal meningitis should be started on secondary prophylaxis with 200 mg daily fluconazole for at least 1 year until their $CD4^+$ count reaches >100 cells/μl and are virologically suppressed.[15] In the absence of follow-up $CD4^+$ measurements in low-income countries, fluconazole is often extended indefinitely. It may take several weeks to months before women recognize their pregnancy status, which may be too late if the highest risk of fluconazole teratogenicity occurs between 3 and 12 weeks gestation, maximal at 4 weeks.[58,85] In a 2004–2008 study from Uganda, 3.5% (54/1519) of enrolled HIV-infected women became pregnant during a 24-month period.[78] Of these, 41% (22/54) were receiving fluconazole 200 mg/day secondary prophylaxis. While there was no excess risk of miscarriage or stillbirth when compared to the placebo arm, it further demonstrates the importance of future research.[86] A Danish study has reported a statistically increased hazard ratio of miscarriage with any fluconazole exposure (HR 1.62 [95% CI: 1.26–2.07]). However (not stated), there was no statistical increased incidence of miscarriage (e.g., one miscarriage per 22.6 women exposed to fluconazole [$n = 3315$] vs. one miscarriage per 23.5 women unexposed [$n = 13{,}246$]). The increased HR demonstrated that miscarriages occurred earlier into pregnancy, but yet the overall incidence of miscarriage between women exposed/unexposed to fluconazole was the same.[79]

We identified seven additional research studies that screened pregnant/breastfeeding women with cryptococcal disease prior to exclusion.[9–11,32–35] These studies, in combination with our own cohorts, demonstrate that cryptococcosis in pregnancy occurs frequently, and best practices for clinical care are unknown. An important limitation of our cases and the published cases in the literature is the lack of clinical information regarding treatment and maternal/fetal outcomes. For instance, in our cohort, fetal outcomes (including HIV and CrAg statuses) were unknown for five participants, and treatment for four of the six asymptomatic CrAg+ women were unknown. Of the 11 published cases, neonatal HIV and CrAg status were not always available. Because pregnant women are routinely excluded from interventional research, this critical information is not routinely collected, which greatly hinders our ability to care for this particular patient population. Overall, both the limited quantity and quality of literature related to cryptococcosis in pregnancy reveal an important knowledge gap and call for future research.

In our study population, we reported good clinical outcomes for pregnant women with cryptococcal meningitis using amphotericin B (0.7–1.0 mg/kg) without high dose fluconazole in the first trimester, and using weekly amphotericin B, in place of fluconazole for cryptococcal antigenemia. Despite having a potentially life-threatening disease, pregnant women with cryptococcosis are routinely excluded from clinical research. Ideally, the benefits of inclusion should be weighed against the high risk of mortality and morbidity from this disease, as blanket exclusions limit advancement in the treatment of pregnant/postpartum women. Given the lack of treatment guidelines for pregnant women with cryptococcosis or other systemic endemic mycoses, a registry is needed to capture the treatment and outcomes of pregnant women.

Supplementary material

Supplementary material are available at *MMYCOL* online.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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