Antenatal infections with *Candida* species

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SUMMARY The clinical, pathological, and microbiological features of 18 pregnancies complicated by intrauterine infection with *Candida* sp. are described. Chorioamnionitis with *Candida* sp. can be recognised macroscopically at birth. Penetration of the umbilical cord and membranes is associated with an intense fetal inflammatory response. The infection characteristically presents in infants of very low birthweight as pneumonia or a skin infection. In nearly every case the organism can be recovered from the gastric aspirate. A case control study showed that there is a striking association between chorioamnionitis caused by *Candida* sp. and the presence of a foreign body (an intrauterine contraceptive device or a cervical suture) in the mother's genital tract in pregnancy. This feature in the perinatal history of an infant of short gestation who exhibits a very high neutrophil count should alert the clinician to the possible presence of chorioamnionitis due to *Candida* sp.

Despite the frequency and ease with which *Candida* species are isolated from the genital tracts of pregnant patients,¹⁻⁴ antenatal fetal infections with this group of organisms are rare. Larroche and colleagues⁵ have reported probable cases of congenital candidiasis, but Benirschke and Raphael⁶ described the first definitive case in which invasion and proliferation within fetal tissues by a *Candida* sp. was detected at birth when they described chorioamnionitis and funisitis in a stillborn infant. Since then at least 30 other cases have been reported,⁷⁻²¹ even though not all cases have had detailed examinations of the placenta and membranes.

This paper adds 18 further cases to the literature. A review of the previously reported cases, and of the clinical features in our infants, reveals a syndrome that differs in many respects from that seen in infections with a haematogenous dissemination of *Candida* sp.

Materials and methods

McMaster University Medical Centre is the regional referral centre for high risk pregnancy for the south central region of Ontario. About 80% of deliveries are to women with high risk pregnancies.

As part of the routine review of placentae from all deliveries in our hospital, 18 cases of *Candida* sp. chorioamnionitis and funisitis were diagnosed between the years 1973 and 1981. During this period about 9000 placentae were received and 3500 examined. The placental and umbilical cord lesions were confirmed with conventional histological

examination using several different staining techniques. Specimens from 4 of the most recently diagnosed cases were submitted for scanning electron microscopical examination as well.

Details of gestation, birthweight, complications of pregnancy, the infant's postnatal clinical course, and laboratory investigations were obtained from the clinical records.

In order to assess the importance of the antenatal and postnatal data a case control study was initiated. For each infant with *Candida* sp. chorioamnionitis a control was sought from the list of all infants delivered in McMaster University Medical Centre from 1977 to 1981. To qualify as a control, the birthweight of an infant had to be within 25 g of that of the case: from the number of infants qualifying for each case, one was selected using random tables. The chart of the control infant was then reviewed to compare the clinical, haematological, and microbiological features with the case of *Candida* sp. chorioamnionitis. Statistical comparison was by Wilcoxon's two sample rank sum test or by the exact probability test of Fisher.

There were 7 deaths in this series and in 6 of these infants a detailed necropsy examination was possible.

Results

Changes in the umbilical cord and placenta. Discrete rounded yellow plaques, the pathognomonic changes^{6-8 11 14 17-19} of *Candida* sp. funisitis, were seen in the umbilical cord and membranes. These lesions varied in size from 0.5 to 2 mm and appeared

in clusters (Fig. 1). Microscopical examination of the affected cords generally showed other minute lesions that had not been identified by the naked eye. In 11 cases the fetal surface of the placenta was covered with a diffuse exudate without specific distinguishing morphological features; in 7 cases small yellow colonies clustered around the insertion of the cord were present and the remainder of the fetal surface of the placenta was spared.

Histological examination showed the subamniotic distribution of the lesions on the cord (Fig. 2). They were strung out on its surface like a necklace. In some areas, these lesions were associated with irregular degeneration of Wharton's jelly, and they were always accompanied by intense diapedesis of fetal inflammatory cells through the walls of the umbilical vessels. In places where the lesions overlaid superficial vessels a distinctive pattern could be seen.

Fig. 1 Umbilical cord showing clusters of small yellow focal lesions on amniotic surface.

Fig. 2 Low power view of transverse section of cord. Note the subamniotic lesions (upper right) strung out along the surface. Papanicolaou stain $\times 16$.

Here those segments of the umbilical vessels orientated towards the superficial lesions showed evidence of fibrinoid change in the media with an accompanying inflammatory cell infiltrate in their wall, but segments of the vessel wall away from the lesions showed far fewer, if any, alterations. These appearances suggested a strong chemotactic influence on the fetal inflammatory cells.

The numbers of organisms present varied considerably from case to case, and even from one lesion to the next in the same case. In some plaques, large numbers of organisms could be identified, proliferating freely on the surface of the cord with little evidence of any significant inflammatory response.

In other plaques, the organisms were ensheathed in fibrin and were far fewer in number (Figs 3 and 4).

As the organisms penetrated the umbilical cord, they evoked a very dense cellular response which was composed of polymorphonuclear leucocytes and mononuclear cells in about equal proportions. The mononuclear cells stained positively with chloroacetate esterase, indicating that they were myelocytes. In the deeper planes of the lesions the organisms were extremely difficult to identify, and they failed to stain as densely as at the surface suggesting progressive destruction of the cell wall.

None of the placentae showed evidence of inflammatory changes affecting the chorionic villi or decidual plate.

Fig. 3 Surface of plaque showing numerous yeasts and pseudohyphae, Gomori methenamine silver $\times 250$.

Fig. 4 (A) Scanning electron micrograph of surface of yeast-rich plaque $\times 2800$. (B) Same plaque as (A), $\times 5600$. (C) Scanning electron micrograph of plaque with very few organisms $\times 2800$. (D) Same plaque as (C) showing a single yeast covered with fibrinous strands $\times 5600$. All illustrations are from the same umbilical cord and show the considerable degree of variation that may be encountered in a single case.

Maternal antenatal clinical features and complications of pregnancy. The details of the antenatal histories of the mothers of the 18 cases are given in Table 1 and compared with those of the mothers of weight-matched controls.

All except one pregnancy were of short gestation, 12 of them less than 28 (range 18–37) weeks; this distribution was almost exactly matched by that of the controls. Seven mothers had experienced previous fetal losses before 20 weeks and in 5 there had been repeated spontaneous abortions. In 6 cases the membranes had ruptured more than 24 hours before

delivery, while in 6 the membranes were still intact one hour before delivery. There was an attempt to inhibit labour with isoxsuprine and sometimes with ethanol in 13 mothers, 5 of whom were given betamethasone in an attempt to lessen the subsequent risk of hyaline membrane disease in the infant. In 8 mothers chorioamnionitis was suspected or demonstrated and antibiotics were administered.

Eight mothers had intrauterine contraceptive devices (copper in 7) present throughout pregnancy. Five mothers, all of them with repeated previous fetal losses, had cervical sutures in place for the treatment of cervical incompetence. When compared with the control group there was a striking predominance in the cases of pregnancies complicated by the presence of a foreign body in the cervix (72% compared with 1%). This difference is highly significant ($P < 0.001$) and is largely attributable to the mothers with intrauterine contraceptive devices ($P < 0.001$). The difference in incidence of cervical sutures did not reach significance ($P = 0.08$) on its own, perhaps because there were fewer patients.

There was a significant difference in the numbers of mothers who had experienced repeated fetal losses ($P = 0.02$) and among these were the mothers who had received cervical sutures. There were no significant differences in the numbers of pregnancies complicated by prolonged rupture of membranes,

Table 1 Features of antenatal and perinatal histories of mothers in whom *Candida chorioamnionitis* was identified compared with controls (* $P < 0.01$ ** $P < 0.001$)

	Cases (n=18)	Controls (n=18)
Maternal age (median) years	25	26
Gestation at delivery (median) (weeks)	25	27
No of previous pregnancies (median)	2	2
No with diabetes	1	0
No with urinary tract infection	0	0
Ruptured membranes >24 hours	6	5
Tocolytic therapy	13	12
Antibiotics in labour	8	3
Steroids in labour	5	4
Intrauterine contraceptive device in pregnancy	8	0*
Cervical suture in pregnancy	5	1
Total foreign bodies in pregnancy	13	1**

Table 2 Neonatal course in infants born from pregnancies in which *Candida* chorioamnionitis was identified compared with controls

	Cases (n=18)	Controls (n=18)
Birthweight median (g)	860	880
Abortion	1	1
Stillborn	1	1
Neonatal death	3	5
Skin rash*	5	0
Pneumonia on chest x-ray film*	5	0
Treated with amphotericin B*	7	0

*Numbers apply to 13 cases and 12 controls surviving first day of life.

diabetes, or urinary tract infections, nor were there significant differences in the numbers of mothers treated with tocolytic therapy, steroids, or antibiotics.

Clinical course. These features are summarised in Table 2. Three infants died before or within an hour of birth, one died at 6 days, and one died of bronchopulmonary dysplasia at 14 weeks.

Of those who survived the immediate perinatal period 4 developed a skin rash and 5 had radiological signs of pneumonic consolidation quite distinct from other forms of lung disease; one of these infants had both the rash and pneumonia. The skin rash was characterised by small papulovesicular lesions with an areola of erythema occurring in clusters which characteristically started on the face and progressed down the trunk. One infant who had neither rash nor pneumonia developed a perforation of the intestine. *Candida* sp. was present in the bowel lumen and blood culture became positive for *Candida* sp. However, no disseminated haematogenous infection was apparent and there was no evidence of vasculitis in the resected segment of bowel. This infant was the only member of our series in whom the blood culture was positive for *Candida* sp.

Three infants, all of whom were greater than 2 kg in birthweight, were asymptomatic.

All infants were treated with a combination of

oral and topical nystatin. In 8 infants in whom clinical and haematological features suggested disseminated infection, systemic amphotericin B (0.25 mg/kg a day) was given as well. This appeared to produce prompt clinical remission of clinical features, although in 3 cases the administration of the drug was associated with episodes of bradycardia and hypotension.

The species isolated were *Candida albicans* in 15 cases and *Candida parapsilosis*, *Candida tropicalis*, and *Candida stellatoidea* in one each of the remaining three. In one case colonies of *Candida* sp. were identified on the cord and placenta while cultures of gastric aspirate and superficial cultures were negative. Of the remainder, 10 out of 13 from whom samples were collected had positive gastric aspirates and 12 out of 14 had positive skin cultures. Fourteen babies had samples cultured from cerebrospinal fluid and blood: all these were negative. All 5 babies with radiological changes of pneumonia had positive endotracheal cultures for *Candida* sp., and the organism was recovered from the skin lesions of all 5 infants presenting with skin rashes. In 13 babies in whom urine was collected (2 from suprapubic aspirates and 11 from bag collections) there was no growth of *Candida* sp. No positive cultures for *Candida* sp. were found in the 14 controls investigated; gastric aspirates, skin, blood, and urine samples were collected from 11 control babies.

Table 3 shows the highest white cell counts and their differentials in babies who survived the immediate perinatal period. Characteristically the white cell counts were highest in the first few days of life; in 10 of our cases the highest counts were recorded within the first 3 days of life. Babies with candidiasis showed extreme increases in white cell counts due largely to a pronounced increase in neutrophils both as segmented forms, band forms, and other immature forms—that is myelocytes, promyelocytes, and myeloblasts. This extreme polymorphonuclear leucocytosis with a marked shift to left exceeds that usually seen in infants of similar gestation with proved bacterial sepsis.²²

Because of the likelihood of introducing sampling

Table 3 Highest recorded white cell counts from 15 cases of *Candida* chorioamnionitis compared with 14 controls

	Candidiasis Count $\times 10^9/l$		Controls Count $\times 10^9/l$		P
	Median	10-90 centile	Median	10-90 centile	
Total white cell count	62.2	23.6-91.0	20.8	15.6-35.7	<0.005
Segmented neutrophils	41.5	8.4-71.6	11.7	4.4-25.0	<0.001
Band neutrophils	2.4	0.2-19.0	0.6	0.0-5.3	<0.005
Immature neutrophils	1.7	0.0-12.8	0.0	0.0-1.1	<0.001
Lymphocytes	8.1	5.3-13.0	5.4	2.9-12.2	<0.02

errors by taking peak values alone, haematological values were taken for each case and control from the 1st, 7th, and 14th days of life: values were used only if full sets of data were available for both cases and controls for the day. We were therefore able to compare the group values of 13 pairs on the 1st day, 9 pairs on the 7th, and 5 pairs on the 14th. The age at which the blood was collected was compared by Wilcoxon's two sample rank test and no significant differences were found between cases and controls: 7 cases and 8 controls had blood samples taken within one hour of birth, and in both groups all but one sample had been collected in the first 6 hours. The results (Figs 5 and 6) confirm the pronounced increase in neutrophils in both segmented and immature forms in infants with candidiasis compared with controls of similar weight and gestation.

Fig. 5 Distribution of segmented neutrophil counts in infants with *Candida chorioamnionitis* compared with controls.

Fig. 6 Distribution of immature neutrophil counts in infants with *Candida chorioamnionitis* compared with controls.

The lymphocyte series showed little or no response to the infection: the difference demonstrated in the peak counts was not significant in the matched counts done on specific days.

Necropsy findings in fatal cases. Of the 5 fatalities in this series, 4 occurred in the early perinatal period, and one after a period of 14 weeks. Necropsy examinations were performed on the bodies of 3 of the 4 perinatal deaths, and on the single infant death.

In the first day perinatal deaths a diffuse pneumonitis was present, and budding yeast forms could be identified in the inflammatory exudate within the airways, most noticeably within the cytoplasm of syncytial giant cells. The stomach in 2 of the infants was filled with a mucoid felted mass which histological examination showed to be made up of numerous budding yeasts and pseudohyphae embedded in inspissated mucus. Otitis media with yeast penetrating the mucosa of the middle ear was identified in one infant and multiple plaques with

pseudohyphae penetrating the oesophageal epithelium was identified in another. There was no evidence of a meningitis associated with *Candida* sp. nor was there any evidence of generalised haematogenous dissemination.

The infant who died at 14 weeks postnatally had been treated with nystatin and amphotericin B. His skin rash had disappeared and the infiltration seen on the x-ray film had resolved several weeks before his death. At necropsy there was no evidence of residual fungal infection: he had succumbed to hydrocephalus, complicating previous intraventricular haemorrhage, and bronchopulmonary dysplasia.

Discussion

Although about 25% of all pregnant women carry the *Candida* sp. organisms in their vagina,¹⁻⁴ intrauterine infections are rare. With the exception of the review of Batista and Pereira,⁹ most of the literature⁵⁻²¹ consists of reports of small series or individual cases. The benefits of a retrospective review and the fairly large number of personally studied cases allow us to stress some features that may be of significance.

A remarkable feature of our series is that the mothers of 13 of the 18 infants had a foreign body *in situ* in the genital tract. The mother of the fetus described by Ho and Aterman¹⁹ was also using an intrauterine contraceptive device. It is known that *Candida* sp. infections can be a complication of indwelling catheters, whether in the urinary bladder or intravascularly,^{23 24} and the belief that the presence of an intrauterine foreign body (either a cervical suture or a contraceptive device) contributed to intrauterine colonisation with *Candida* sp. has some plausibility. Many of the cases reported in the literature predate the widespread use of intrauterine contraceptive devices. It is possible that more cases of *Candida* sp. infections will occur in instances where, despite the use of an intrauterine contraceptive device, a pregnancy occurs. Furthermore, in instances where a foreign body is present in the uterus, prolonged rupture of membranes would *not* be a necessary factor to produce an intrauterine infection.

A review of the previously reported cases reveals several patients who, like two-thirds of our patients, did not have evidence of ruptured membranes in excess of a duration of 24 hours.^{6-9 12-15 21} As far as can be ascertained, in none of the cases reported by Batista and Pereira⁹ can prolonged rupture of membranes be implicated in the development of chorioamnionitis, since the organism was recovered from amniocentesis in 12 of 55 patients. Clearly,

prolonged rupture of membranes, classically regarded as one of the main predictors (and cause) of chorioamnionitis, is not a reliable indicator of the likelihood of developing *Candida* sp. chorioamnionitis. It appears that *Candida* sp. may be able to penetrate 'intact' membranes, even though the pathogenesis is not understood.

Infection with *Candida* sp. can be diagnosed at birth by a careful examination of the cord and membranes. The discrete yellow plaques and nodules are characteristic, and the necklace-like arrangement of the cord lesions is one with which obstetricians as well as neonatal paediatricians should be familiar. (*Monilia*, an alternative name for this group of yeasts is derived from Latin: a necklace.) The nature of the lesions can be confirmed by a rapid section if necessary, but the importance of identifying them with the naked eye cannot be overemphasised, since the appropriate laboratory investigations to confirm the diagnosis can be initiated with little delay, and the correct interpretation of clinical and radiological findings is facilitated.

We believe that the necropsy findings in our perinatal deaths and in other reported cases are of interest. Even with widespread congenital disease, the pattern of organ involvement suggests slowly spreading infection affecting the skin and contiguous mucosal surfaces (pharynx, oesophagus) with spread due to aspiration and swallowing of contaminated material. We did not see evidence of haematogenous dissemination at necropsy. In 9 of our cases there was gradual progression of infection despite negative cultures from traditional deep sampling sites. Cultures taken from traditional sites of investigation for neonatal bacterial sepsis—that is blood, suprapubic bladder tap, cerebrospinal fluid—may remain negative despite the presence of severe generalised *Candida* sp. infection.

Our decision to use a systemic antifungal agent in some of these babies may be questioned. However, this decision was made on the basis of their deteriorating clinical state, despite adequate antibacterial therapy, and the knowledge that there was evidence of *Candida* sp. chorioamnionitis and funisitis. Treatment with amphotericin may itself be hazardous, and we are not in a position to recommend its universal use in this condition.

The 3 largest and most mature infants in our series showed no evidence of any infection during their postnatal stay in the nursery. The data in our series and in other reports suggest that the outcome and course of congenital *Candida* sp. infections are related to the gestational age of the infant. Combining the previously reported cases with those in

our series it would appear that 3 possible modes of presentation and clinical outcome exist. The most immature infants may be stillborn, or very early neonatal deaths, and may have widespread pneumonia and sometimes other surface infections (dermatitis, vulvovaginitis, balanitis, conjunctivitis),¹⁰ but without evidence of haematogenous dissemination at necropsy. It is worth noting that, with the inclusion of cases from the present series, 9 of the 13 perinatal deaths have occurred in infants of 28 weeks' gestation or less. In one of these cases,⁶ a lethal malformation was present (anencephaly) while in many of the others, severe immaturity was an obvious contributing factor; this was discussed in detail by Ho and Aterman.¹⁹

A less severely affected group of infants may present with surface infections as described above and may require topical antifungal therapy. Their condition may deteriorate with evidence of pneumonia, and systemic antifungal therapy may be indicated. In the accumulated literature and present series, in 20 of the 24 infants with such a pattern of presentation the gestational age was between 29 and 36 weeks. The haematological abnormalities in our infants suggest a method of monitoring the progress of disease. The presence of increased white cell counts, with very high levels of segmented neutrophils and immature cells in the peripheral blood might alert the clinician to the diagnosis and could be used to follow the response to treatment.

The least severely affected group, despite evidence of chorioamnionitis and funisitis, will show no evidence of any other infection and will be asymptomatic. Of the 5 infants in the literature and this series who were asymptomatic, 3 had a gestational age in excess of 37 weeks.

It could be argued that the different patterns of response to *Candida* sp. infections are due to a variable degree of immunological maturity. Our findings at necropsy indicate that an appreciable cellular response to the presence of *Candida* sp. in the lungs exists, and there is ample evidence of a fetal cellular response in the cord and membranes and in the peripheral blood. Morphological studies alone however, do not constitute an accurate assessment of immunological function, and a complete picture of the immune response in fetuses and neonates to *Candida* sp. infections could only be answered by a detailed prospective study. Any such investigation would have to take into account the fact that antibodies to *Candida* sp. that may be present in the umbilical circulation could reflect anti-*Candida* sp. antibodies of IgG type in the mother.²⁵

The syndrome seen in congenital candidiasis is very different from that seen in widespread haemato-

genous dissemination of *Candida* sp.^{23 24 26 27} There is at least one case of congenital candidiasis however, that eventually developed into a blood disseminated disease.²⁰ While there was no mention of the placenta, membranes, or cord in this case, *Candida* sp. was seen in the gastric aspirate at birth. The probable significance of this finding does not appear to have been appreciated, despite the development of respiratory distress and radiological evidence of an aspiration syndrome. *Candida* sp. was isolated from the endotracheal tube several days later, but the infant then developed a meningitis and arthritis, and was treated successfully with amphotericin B. It would seem to us that some cases of 'congenital candidiasis' could develop a disseminated, haematogenous pattern of involvement of other organs, as exemplified by the case cited above. The true number of such cases would be impossible to assess retrospectively, without detailed knowledge of the state of the fetal organs.

This series of 18 cases shows that congenital infections with *Candida* sp. can be anticipated by their association with foreign bodies in the genital tract in pregnancy and diagnosed by careful examination of the cord and membranes in the delivery room. An infant of very low birthweight who develops a very high neutrophil count with immature forms may well be infected with *Candida* sp. Close co-operation between obstetric and paediatric staff in the perinatal period will promote the early recognition and treatment of this disease.

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