

## Coccidioidomycosis as a Complication of Pregnancy

J. E. VAUGHAN, M.D., and HALL RAMIREZ, M.D., *Bakersfield*

### SUMMARY

*Records of 33 cases of coccidioidomycosis occurring during pregnancy were reviewed. In this group the incidence of dissemination of the disease was considerably greater than the reported incidence of dissemination in all cases of coccidioidomycosis.*

*The incidence of dissemination was higher in the patients who contracted coccidioidomycosis late in pregnancy than it was in those in whom onset of the disease occurred earlier in gestation; but dissemination occurred in all Negro patients in the group, regardless of the time of onset during pregnancy.*

*The chief complicating effect when onset was in the first trimester of pregnancy was a tendency to abortion. In cases in which onset was in the third trimester, the incidence of premature labor was extremely high.*

*There was no evidence of congenital infection in any of the babies, but in one case invasion of the placenta by coccidioidal spherules was observed.*

COCCIDIOIDOMYCOSIS occurring during the course of pregnancy has received little comment in the current literature until recently.<sup>9</sup> The work of Gifford<sup>5</sup> and Dickson<sup>4</sup> stimulated further study of the disease. Smith<sup>11</sup> and his co-workers have contributed much to present knowledge. The epidemiology,<sup>12</sup> the importance of the coccidioidin skin test,<sup>14</sup> the extent of the endemic area and the introduction of serological tests in the diagnosis and prognosis of the disease<sup>13</sup> are some of the important contributions. The knowledge that merely driving through an endemic area may result in infection adds to the significance of the disease in differential diagnosis in the western states. The purpose of this presentation is to show the effect of the disease on the course of pregnancy and on the offspring.

Since reporting of non-disseminating coccidioidomycosis is not required, knowledge of its association with pregnancy is incomplete. Case histories of 33 cases of coccidioidomycosis occurring in pregnancy in the period 1942-1949 were obtained from physicians and hospital records in Kern County. Of these, 28 occurred in the 1946-1949 period. The diagnosis in each instance was confirmed by clinical,

laboratory, biopsy, and in some instances, autopsy evidence. This presentation will consider mainly the 28 cases that occurred in the four years 1946-1949. During that period there were 25,328 births, live and stillbirths, recorded in Kern County. Thus, the incidence of known cases of coccidioidomycosis was approximately one in 900 pregnancies. Hertig<sup>7</sup> in a study of abortion concluded that spontaneous abortion occurred in approximately ten per cent of all pregnancies. On this basis the corrected incidence of infection would be approximately one in 1,000 pregnancies. It is significant, however, that three of the four maternal deaths reported in Kern County for the year 1948 were due to disseminated coccidioidomycosis. Reaction to coccidioidin skin tests done routinely at the time of first prenatal visit was positive in approximately 40 per cent of 800 private cases. Dissemination did not occur in any of the cases in which there was previous coccidioidal infection. Cohen and Burnip<sup>2</sup> reported positive reaction in 47 per cent of mothers at time of delivery in county hospital cases.

Early in this study the authors were impressed with the apparent severity and rapidity of generalized dissemination of the disease when it occurred in the latter part of pregnancy. For this reason the cases are divided into four groups: first, those in which the patients were known to have coccidioidomycosis preceding onset of pregnancy; second, those in which coccidioidomycosis was contracted during the first trimester of pregnancy; third, those in which coccidioidomycosis was contracted during the second trimester; fourth, those in which the disease was contracted during the third trimester.

In Group I (known coccidioidomycosis preceding pregnancy) there were five patients, all of whom recovered (Table 1). Tests carried out on all of these patients showed the presence of complement fixing antibodies without the presence of precipitins before onset of pregnancy. There were complications in four of the five cases: In one case spontaneous abortion occurred at two and one-half months, in two others there was threat of abortion, and one patient had a pulmonary hemorrhage in the first trimester with an interruption of pregnancy. Two patients were delivered of viable infants at term; neither of the babies showed evidence of coccidioidomycosis, but in one there was evidence of humoral or passive transfer of antibodies through the placenta. Reaction to a subsequent coccidioidin skin test was negative.

In Group II (coccidioidomycosis occurring during first trimester) there were 12 patients—ten Caucasians, one Negro, one Mexican (see Table 2). The Negro patient died, the others recovered. There

Presented before the Section on Obstetrics and Gynecology at the 79th Annual Meeting of the California Medical Association, San Diego, April 30-May 3, 1950.

was no evidence of coccidioidomycosis in any of the babies.

CASE REPORT

A Negro woman 20 years of age (Case 12, Table 2) was admitted to hospital when approximately three months pregnant, with bleeding and cramping. Spontaneous abortion followed. Skin lesions of short duration were noted. Coccidioidal spherules were observed in biopsy of aspirated material. Reaction to a complement fixation test was +++ at 1:128 dilution. Precipitin reaction was ++++ at 1:40 dilution. A diagnosis of disseminated coccidioidomycosis of

fairly recent origin was made. Actidione, a fungistatic antibiotic, was given. The skin lesions healed rapidly, but approximately three months later the patient died.

Buss, Gibson and Gifford<sup>1</sup> noted that although the non-white group constitutes only about 8 per cent of the population in Kern County, 50 per cent of coccidioidal dissemination occurs in that group.

Gifford<sup>6</sup> called attention to the fact that in recent years more of the non-granulomatous, non-fatal type of coccidioidal disease had been reported, with more cases in women than in men.

TABLE 1.—Patients With Known Coccidioidomycosis Preceding Onset of Pregnancy

Case	Age	Date of Onset	Race	Last Menstrual Period	Serology			Precip.	Complications During Pregnancy	Outcome	
					Comp.	Fixation	Dilution			Mother	Infant
					1:2	1:4	1:8				
1	32	May 1945	White	Nov. 1945	++++	+	0	0	Threatened ab. 3rd month	Recovery	Term viable. No evidence of coccid.
2	24	1942	White	Oct. 1949	++++	0		0	Cavity in left apex. No other complications.	Undelivered	Undelivered
3	34	Oct. 1947	White	March 1949	++++	++	+	0	Spont. abortion 2½ months.	Recovery	.....
4	26	April 1948	White	May 1948	++++	+	+	0	Extreme malaise. Uterine contractions.	Recovery	Term viable. Skin test neg. Passive transfer of antibodies
5	21	Feb. 1947	White	May 1947	++++	0	0	0	Pulmonary hemorrhage 1st Trimester	Recovery	Therapeutic abortion

TABLE 2.—Cases in Which Coccidioidomycosis Was Contracted During First Trimester of Pregnancy

Case	Age	Race	Complications During Pregnancy	Outcome	
				Mother	Infant
1	18	W	None	Recovery	Term viable. No evidence of coccidioidomycosis.
2	23	W	None	Recovery	Term viable. No evidence of coccidioidomycosis.
3	23	W	Threatened abortion, 2nd month	Placenta previa bleeding at term. Section. Recovery.	Term viable. Skin test for coccidioidomycosis negative.
4	25	W	None	Recovery	Term viable. Skin test for coccidioidomycosis negative.
5	26	W	Premature separation of placenta	Section. Recovery	Stillbirth. No evidence of coccidioidomycosis.
6	17	W	None	Recovery	Term viable. No evidence of coccidioidomycosis.
7	29	W	Erythema nodosum. Extreme malaise. Agglut. and Precip. disappeared.	Undelivered, condition good.	.....
8	21	W	None	Recovery	Term viable. No evidence of coccidioidomycosis.
9	20	W	Threatened abortion	Recovery	Term viable. No evidence of coccidioidomycosis.
10	23	W	None	Recovery	Term viable. No evidence of coccidioidomycosis.
11	22	Mexican	None	Recovery	Term viable. No evidence of coccidioidomycosis.
12	20	Negro	Spontaneous abortion. Dissemination. Treated with actidione.	Fatal	.....

In Group III (coccidioidomycosis occurring during second trimester) there were five patients, three of whom completely recovered without dissemination. Dissemination occurred in two patients, one of whom died. The other was still alive two years after dissemination occurred (see Table 3).

#### CASE REPORTS

Coccidioidomycosis developed in a 34-year-old white woman during the fifth month of pregnancy (Case 3, Table 3). Dissemination to the meninges occurred shortly thereafter. The patient was given diethylstilbestrol for control of uterine contractions, and, in addition, actidione. A viable infant was delivered spontaneously at term. Results of simultaneous serologic studies on mother and infant were interpreted as being suggestive of humoral transfer of antibodies through the placenta. There was no pathologic evidence of coccidioidal granuloma of the placenta. At the time of this report the patient was still living, but studies of the spinal fluid gave evidence of continuing infection. Later, a complement fixation test of blood from the infant showed a doubtful reaction with 1:2 dilution of serum.

Generalized coccidioidal dissemination developed in a Negro woman 22 years of age in the fifth month of pregnancy. The condition of the patient deteriorated rapidly in spite of all treatment, including actidione. A viable infant was delivered prematurely. Serologic studies gave evidence of passive transfer of maternal complement fixing antibodies to the infant. In pathologic examination of the placenta numerous large and small lesions were observed, both in the decidua and in the chorionic villi. The lesions were necrotic, some appearing caseous, others frankly purulent. These lesions were filled with spherules of *coccidioides immitis*. Spherules were of all sizes and stages of development. Some large spherules contained encapsulated endospores. Reaction to coccidioidin skin tests of the infant were negative. In a second serologic study, pronounced decrease in the titer of complement-fixing antibodies was noted. The infant died six weeks after birth. All tissues were examined pathologically and no evidence of coccidioidal granuloma was observed.

Cohen<sup>3</sup> reported a case of coccidioidal infection in an infant in the second week of life whose mother had San Joaquin fever during pregnancy. The placenta was not examined. Smale and Birsner<sup>9</sup> reported one case of coccidioidal granuloma of the placenta. However, no information was obtained regarding the mother or the infant.

In Group IV (coccidioidomycosis occurring during the third trimester) there were 11 patients—six Caucasians, four Negroes and one Chinese. Four of the Caucasians had no complications and were delivered of full-term viable infants without evidence of coccidioidomycosis. Generalized dissemination occurred in the other two, who were delivered of premature viable infants; there was no evidence of coccidioidomycosis in the infants. A similar course developed in the case of the one Chinese patient, who delivered a premature viable infant. In four cases in Negroes there was rapid dissemination. One patient was given actidione without any change in the course of the disease. It seems of significance that in Group IV there was a greater number of cases of generalized dissemination, and that dissemination occurred in two white women. Those with dissemination invariably delivered prematurely. Other than passive transfer of complement-fixing antibodies, there was no evidence of coccidioidal granuloma in offspring or in the placenta examined (see Table 4).

#### DISCUSSION

Smith<sup>10</sup> stated that dissemination occurs in not more than one case in five hundred or a thousand cases of coccidioidomycosis. Even taking into account the probability that two-thirds of primary infections are not diagnosed, the incidence of dissemination in this series still must be considered high. It was particularly high among patients who contracted the disease in the third trimester: Seven of the 11 patients died a short time after onset. Fatal dissemination occurred in all four of the Negro patients in this group.

Page and Bayers<sup>8</sup> reported a case of coccidioidomycosis which primarily involved the uterus, the fallopian tubes and one ovary. One other similar case had previously been reported. In no case in the present series in which autopsy was carried out was there pathological evidence of dissemination to the uterus, tubes or ovaries. However, multiple implants on the parietal and visceral peritoneum were frequently observed. In one case multiple areas of invasion by the spherules were noted in the placenta, but there was not, in this case or in any other in the

TABLE 3.—Cases in Which Coccidioidomycosis Was Contracted During Second Trimester of Pregnancy

Case	Age	Race	Complications During Pregnancy	Outcome	
				Mother	Infant
1	24	W	None	Recovery	Term viable. No evidence of coccidioidomycosis.
2	25	W	In car accident. Threatened abortion, premature labor.	Recovery	Premature non-viable. No evidence of coccidioidomycosis.
3	34	M	Acute onset. Developed meningitis fifth month. Uterine contractions treated with stilbestrol and actidione.	Alive. Still has cells in spinal fluid.	Term viable. Passive transfer of antibodies. No evidence of coccidioidomycosis.
4	26	W	None	Recovery	Term viable. No evidence of coccidioidomycosis.
5	22	Negro	Cutaneous lesions fifth month. Meningitis. Treated with actidione.	Fatal	Premature viable. Passive transfer of antibodies; spherules in placenta. Later autopsy of infant, no evidence of coccid.

series, any evidence of congenital infection of the infant. As far as could be determined, no congenital anomalies occurred as a result of the coccidioidal infection.

#### TREATMENT AND MANAGEMENT

Dyspnea, during the acute illness, which is commonly out of proportion to the demonstrable pathologic changes in the chest, is greatly relieved by rest. Rest appears to be the one important treatment. This should be carried out just as in cases of tuberculosis until the patient has recovered clinically. Blood sedimentation rate determinations and serological tests indicate the progression or regression of the lesions and may be used as a guide in controlling activity. The authors have found that much of a patient's fears concerning the disease can be relieved by telling him the following facts: First,

the diagnosis of acute coccidioidomycosis cannot be established on the basis of positive reaction to a skin test alone; second, relapses do not occur after recovery from the disease; third, no cases of reinfection have been reported; and, fourth, it is not necessary to move from an endemic area to recover.

In an endemic area it is recommended that a coccidioidin skin test be done on pregnant women at the time of the first prenatal visit. If the reaction is positive, x-ray studies of the chest and serological tests should be carried out to determine the extent of the disease. Patients in whom symptoms of upper respiratory tract disease develop during pregnancy should be carefully studied for coccidioidal infection even though the reaction to the initial skin test was negative. A regimen of strict rest may forestall dissemination.

2109 Eighteenth Street.

TABLE 4.—Cases in Which Coccidioidomycosis Was Contracted During Third Trimester of Pregnancy

Case	Age	Race	Complications During Pregnancy	Outcome	
				Mother	Infant
1	29	W	Generalized dissemination, premature labor.	Fatal	Premature viable, coccid. skin test negative.
2	23	W	None	Recovery	Term viable. No evidence of coccid. Coccid. negative.
3	31	W	Generalized dissemination, premature labor.	Fatal	Premature (8½ mo.) viable. No evidence of coccid. Coccid. skin test negative.
4	24	W	None	Recovery	Term viable. No evidence of coccid.
5	25	W	None	Recovery	Term viable. No evidence of coccid.
6	21	W	None	Recovery	Term viable. No evidence of coccid.
7	24	Chinese	Generalized dissemination. Meningitis. Premature labor.	Fatal	Premature viable. No evidence of coccid. Skin test negative.
8	37	Negro	Generalized dissemination.	Fatal	Stillbirth. No evidence of coccid. recorded.
9	28	N	Generalized dissemination, premature labor.	Fatal	Premature viable. Passive transfer of antibodies. No evidence of coccid.
10	27	N	Generalized dissemination.	Fatal. Died undelivered.	Infant—no evidence of coccid.
11	19	N	Generalized dissemination, premature labor. Treated with actidione.	Fatal	Premature (8 mo.) viable. No evidence of coccid.

TABLE 5.—Summary of Fatal Cases

Case	Age	Race	Trimester of Onset	Outcome	Infant
1	29	White	3rd	Generalized dissemination	Premature viable, coccid. negative.
2	31	White	3rd	Generalized dissemination	Premature viable (8½ mo.) coccid. negative.
3	24	Chinese	3rd	Generalized dissemination	Premature viable. Coccid. negative.
4	37	Negro	3rd	Generalized dissemination	Stillbirth, no report on coccid.
5	28	Negro	3rd	Generalized dissemination	Premature viable, passive transfer of antibodies, no evidence of coccid.
6	27	Negro	3rd	Generalized dissemination	At term. Died undelivered. No evidence of coccid.
7	19	Negro	3rd	Generalized dissemination. Premature labor.	Premature viable (8 mo.). No evidence of coccid.
8	22	Negro	2nd	Generalized dissemination	Premature (7 mo.) viable, passive transfer antibodies. Coccid. negative.
9	20	Negro	1st	Spontaneous abortion 1st trimester. Generalized dissemination.	Spontaneous abortion (2½ mo.)

## ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance given by Dr. Charles E. Smith, Chairman of the School of Public Health, University of California; Dr. William C. Buss, Health Officer, Kern County Department of Public Health; Dr. Myrnie A. Gifford, Assistant Health Officer, Kern County Department of Public Health, and by the physicians of Kern County who contributed case reports.

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