SYPHILIS AND PREGNANCY

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IN 1905, Schaudinn, a protozoologist, looking through a microscope, saw the Spirochæta pallida and announced the etiology of syphilis. Two years later Wassermann, Neisser and Bruck developed the serological test, making the diagnosis possible. In 1910, Ehrlich stated that the infection could be cured with salvarsan.

Preventative medicine probably never has been favored with three such epoch-making researches as the three announced during those five years. Armed with these excellent weapons, much should have been accomplished but relatively little has been done in the prevention and treatment of syphilis in the pregnant woman. There would be no infected newborn babies if their mothers were free of syphilis.

Parran has stated that 60,000 babies are born in the United States every year with congenital syphilis. Our rate for congenital syphilis alone is twice as high per thousand of our population as is Denmark's rate for syphilis of all types. The incidence of syphilis in obstetrical clinics varies from 1 to over 30 per cent. There is wide variation in the incidence of the infection in clinics of the same city, depending upon the difference in the clinic clientele.

A complete physical examination often gives no indication that the pregnant woman has syphilis. A chancre, during gestation, has not been seen in our obstetrical clinic during the past nine years. An infective lesion of the vulva would probably be noted by the patient. The vagina is rarely involved due to the protection of the stratified squamous epithelium. The cervix is the most common location of the chancre. The Fallopian tubes are rarely involved and the ovary practically never.

Unfortunately, unlike gonorrhea, which causes sterility, the syphilitic woman is as fertile as the nonluetic.

About eight days following fertilization, the ovum becomes implanted in the decidua. The corpus luteum develops and reaches its greatest growth at the third month. At this same time the placenta begins to function. The trophoblast is soon differentiated into an active layer of Langhans and a syncytium. In the middle of pregnancy, the Langhans' layer thins out and finally disappears, leaving a thin syncytium. Possibly, the two layers, which early are luxuriant and active, act as the barrier which prevents the spirochæta from invading the fetus before the fifth month. In only one case, Trincisse found the spirochæta in the Langhans' layer; however, in ten cases the organism was noted in the syncytium. Fetal infection after the fifth month is common. Pregnancies which terminate in the first trimester occur as frequently in the serological negative group as in women with a positive serology. It therefore is believed that spirochætal infection does not cause an early abortion. The organism has not been recovered from an early fetus.

The absence or mildness of syphilitic infection during pregnancy suggests the probability of a beneficial effect during gestation.

Brown and Pearce injected a testicular emulsion of Spirochæta pallida intradermally in eight pregnant rabbits, and into an equal control series of three normal females, two females in heat and three males. Definite lesions with marked adenitis were present in all the controls at the end of the third to the fourth week. Four of the eight pregnant females inoculated in the same way failed to show any evidence of infection. Three showed slight infiltration at

the site of inoculation with no lymphadenitis. The one successfully inoculated pregnant rabbit was in the middle of her pregnancy.

Likewise, in women, there is apparently a protective mechanism, and this is especially true in those women who have become pregnant since their infection.

White and Davis, in their study of cardiovascular syphilis noted male infection to be five times more common than in the female. Turner observed both cardiovascular and neurosyphilis to be over twice as frequent in male as in female patients. Moore noted a lower incidence of neurosyphilis in women who had become pregnant since infection than in those who had not. Solomon, studying pregnancy histories in 559 syphilitic women admitted to the Boston Psychopathic Hospital, found that 44 per cent of those with cerebrospinal syphilis had never been pregnant, and concluded that women with this lesion were either infected with a severe neurotrophic strain of organism which affected child bearing, or that women who had become pregnant received some protection against neurosyphilis. The Cooperative Clinic Group, reporting the results of treatment in 591 cases of latent syphilis in females, noted 42.4 per cent of 283 who were pregnant obtained a satisfactory result, while only 29.7 per cent of 303 nonpregnant women had a favorable outcome; 18.4 per cent of the former and 42.2 per cent of the latter were Wassermann fast.

DIAGNOSIS

In taking histories of syphilitic women, it is surprising how few are aware of their infection. To depend solely on the patient's observation of primary or secondary lesions would result in the failure to treat about 90 per cent. Since practically all are masked or in the latent stage, the diagnosis must be made by a routine serological test.

While there is no typical syphilitic obstetrical history, succeeding pregnancies often tend to be carried nearer to term. Late abortions, premature or full term stillbirths should arouse suspicion and an effort made to determine the cause of fetal death. All syphilitic mothers do not transmit the infection to their children, even if untreated. The time element from maternal infection to the delivery of her child is important. The older the infection, the less virulent it is. There is, therefore, less chance of transmitting the spirochæta to the child in utero. If the baby is luetic, the mother also is luetic. The father may or may not have the infection. In this state until 1938, when premarital serological tests were made a prerequisite to marriage, both contracting parties could have been syphilitic, neither having necessarily infected the other. In our clinic, 50 per cent of the husbands of patients receiving prenatal syphilis therapy had neither a positive serology nor gave a history of treatment.

Unfortunately, too much emphasis has been placed on the so-called false positive of pregnancy. Following the development of the Wassermann test many conditions were thought to give a positive reaction. Among these were tuberculosis, malignancy, pregnancy, anesthesia, diabetes, scarlet fever and jaundice. However, as the technic of this test has improved, and trained serologists have become responsible for its interpretation, the incidence of false positive reactions has markedly decreased. Hinton did serological tests on 3,701 U. S. Naval aviation students. Only .56 per cent gave a positive reaction. However, of 862 inmates of The Massachusetts Reformatory for Women whom he studied, 40.49 per cent gave a positive reaction. Eagle tested the blood of 1,000 medical students, nurses and hospital employees, and only one was positive. An examination of this person revealed a chancre. A positive serological test performed by a competent serologist, especially if repeated, means syphilis.

Fordyce and Rosen believed that a Wassermann test done on blood taken just

before delivery is unreliable, and that a weakly positive reaction may occur in normal women during pregnancy. In this connection, 200 women having a negative blood serology in the prenatal clinics at the Kings County Hospital and The Long Island College Hospital were investigated. Blood was taken in the group during labor and tested by the Wassermann complement fixation technic, using two different cholesterolinized antigens. At Kings County Hospital all reports were negative. A parallel group tested by two different flocculation tests, the Hinton and Kline, at The Long Island College Hospital likewise remained negative during labor.

That errors occur in serological investigations is admitted. Incorrect labelling of specimens, errors in typing reports, duplication of names and errors in laboratory technic may be mentioned. Then again, the serum may contain some unusual factor.

Some diseases, such as the following, may possibly give a false positive:

1. *Yaws.* This is an infection closely related to syphilis, caused by the Spirochæta pertenuis. It is non-venereal, although transmitted by contact, affecting chiefly children. It is limited to the tropics. Both complement fixation and flocculation tests will give a positive reaction. Morphologically, the Spirochæta pertenuis cannot be differentiated from Spirochæta pallida.

2. *Leprosy.* A positive serology has occurred in patients suffering from this malady. Investigators have reported marked variations in its incidence. Kolmer and Denny had no false positive reactions in 159 cases. Eagle states that duplicate samples of serum from fifty lepers tested by four modifications of the Wassermann technic and nine different flocculation tests gave from 40 to 76 per cent positive reactions. His series was selected as non-syphilitic.

3. *Malaria.* This disorder shows variations in the reports. In only one series the Wassermann or flocculation test was positive in about 30 per cent. Other reports show less than 1 per cent positive.

4. *Trypanosomiasis.* While this infection has been reported to give a false positive, more evidence is needed.

5. *Relapsing fever* in Europe caused by treponema recurrentis, described by Obermeir in 1868, occasionally gives a confusing reaction.

6. *Infectious Mononucleosis.* It has been noted in this disease that the serum contains an increased amount of heterophile antibody, and a false positive may be caused not by reagin but by an excess of amboceptor.

Before a diagnosis of syphilis is made, the test, if positive, should be repeated. A flocculation, as well as a complement fixation test is valuable. If doubt still exists, repeat in another laboratory. A positive complement fixation and flocculation test indicates that the serum contains reagin, which is a product of infection by the Spirochæta pallida. Eliminating the above mentioned possibilities of false positive reactions, a positive serum which has been confirmed is sufficient evidence for the diagnosis and treatment of syphilis.

PROVOCATIVE

Often one is confronted with a history which does not suggest syphilis yet the blood serology is weakly positive. To institute therapy unnecessarily is unwarranted. On the other hand, failure to protect a fetus in utero of a syphilitic woman is inexcusable. Today, a child has the right to be born without syphilis and may hold the physician responsible for neglect if the infection is not diagnosed and treated.

In doubtful cases of syphilis, we have used as a provocative injection 0.3 Gm. of neoarsphenamine in 10 cc. of freshly distilled water given intravenously. A serological test is done on blood taken one, four and eight days subsequently. If in the tests the reaction has increased from a low to a high one, treatment is indicated in the interest of the unborn child. The

following case may be mentioned as an example of the procedure:

A multipara had an admission serology of 1 plus. The test was repeated showing 2 plus. The provocative injection increased the reaction to 4 plus in the three specimens of blood taken one, four and eight days subsequently. Examination of her two children revealed a positive serology, as did that of her husband. The unborn child, in whose interest the test was performed, was, in the meanwhile, delivered. *X*-ray revealed positive leutic long bone changes. The entire family has syphilis and is now undergoing treatment.

It has been stated that, in the absence of syphilis, the injection of an arsenical would change a negative serology to a positive one. This has not been our experience. Recently, in the Prenatal Clinic of The Long Island College Hospital, we routinely gave this provocative injection to 400 pregnant women with negative Hinton and Kahn tests. Blood taken one, four and eight days after the provocative injection revealed that the Hinton and Kahn tests remained negative in each of the 400 patients.

While, probably, there is no false positive of pregnancy, there may be a false negative. McCord has autopsy material in which the organisms of syphilis were demonstrated in 221 abortions and babies of all periods of gestation. The Wassermann during pregnancy or in labor was negative in 29 per cent of these mothers. In 175 colored stillbirths in all periods of gestation, he noted syphilitic bone changes in thirty-seven babies, or 20 per cent. The maternal Wassermann was negative in sixteen, or 43 per cent.

Whether a husband can infect the fetus directly by Spirochæta pallida in the seminal fluid, while the mother escapes infection, has been discussed for two hundred years.

While an ovum in the Fallopian tube is approached by many spermatozoa, only one shall gain admittance. Where the male cell penetrates the ovum, the vitelline membrane loses continuity and the spirochæta enters. As the walls of the membrane again close, it is so timed that the locomotive portion of the male cell is detached. The ovum is now impervious to all other cells. If the spirochæta were able to enter the ovum with the spermatozoan, its length, about three times that of the active factor of a spermatozoan, would probably be unable to enter completely, and the cytoplasm of the cell would be disturbed by its movements. Slight disturbances of cytoplasm tend to malformation and anomaly. It is infrequent that we find the latter in the syphilitic newborn.

Kemp analyzed his own cases and reviewed the literature of examinations of seminal fluid. Semen of individuals who knew when their infection was contracted was examined for the spirochæta by dark field examination, silver staining or animal inoculation. In sixty-seven individuals, the majority of whom had untreated florid secondary infection or mucocutaneous relapses, treponema were found in thirteen, or 19.4 per cent. However, in fifty-two individuals with late syphilis, only one case showed the spirochæta.

Body fluids, even blood, do not necessarily transmit the infection. Blood transfused into another from donors with a positive serology may or may not transfer the spirochæta. In one case in our clinic, syphilis was transmitted by a donor who had contracted the disease within the previous six months. In another case, an emergency transfusion of blood from the husband was given. The laboratory eventually reported his blood 4 plus, which remained the same on the repeated test. We have followed this recipient for years with many blood tests, and they have all remained consistently negative. The difference in these two cases is one of duration of the infection in the donor. It is not a question of positive serology, but whether, during the actual mechanical transfer of blood from donor to recipient, the fluid contains the spirochæta. McNamara knowingly transfused nine patients with blood of syphilitic donors. Five received blood

by one transfusion; three from two different donors, and one from three donors. In the follow-up of the recipients, neither serological nor clinical evidence of the infection was demonstrable.

TREATMENT

Treatment during pregnancy is directed primarily in the interest of the child in utero. Accordingly, the mother's syphilis is secondary. The limited amount of therapy during pregnancy will have but small effect on the maternal infection.

The fetus apparently is protected against invasion of the spirochæta during the first five months of gestation. McCord failed to find any organism in a dead syphilitic fetus weighing less than 100 Gm., the average weight at the fourth month. It was in the seventh, eighth and ninth-month fetus that the spirochæta was most often found.

Treatment instituted early is directed to *prevent* the infection reaching the fetus. Therapy begun late is intended to *treat* the infected fetus in utero. About 85 per cent of our cases are not seen until the latter half of pregnancy.

Snyder and Speert injected neoarsphenamine in rabbits and noted a progressive increase in the rate of placental transmission of arsenic to the fetus as the pregnancy approached term. After separating the maternal and fetal placental portions, they noted in the fetal part a total amount of arsenic six times as great as in the maternal portion. Within an hour following injection into a rabbit at term, a placental study revealed a larger amount of arsenic in the placenta than was transmitted to the fetus. Gradual liberation of arsenic from the placental reservoir to the fetus was revealed by the much higher content of arsenic in the fetus twenty-four hours following injection.

In four pregnant women receiving neoarsphenamine, Kraul and Bodnar noted arsenic in the three fetuses born in the latter part of pregnancy. In the fetus born at the sixth month, no arsenic was found. That arsenic or its derivatives pass the placental barrier was observed by Eastman, who found a relatively large amount in the meconium and a relatively small amount in the blood of a newborn.

Too often, a patient seen late in pregnancy fails to receive treatment because it is believed that no benefit will result. It is never too late to treat, even though the chances are in favor of fetal infection. A relatively small amount of the arsenical given late in pregnancy is more efficacious than when given in the first five months.

From the obstetrical viewpoint it would be in the interest of the fetus in utero to assume the dictum that once a syphilitic mother, always a syphilitic mother. While it is true that those who have been well treated would probably deliver non-syphilitic children, it is apparent in taking histories on infected mothers that a large number have received inadequate treatment. Even if the Wassermann be negative, the patient may have a syphilitic child.

In spite of the extra load upon the emunctories, the pregnant syphilitic mother tolerates treatment well. By keeping alert for obstetrical complications and realizing the potentialities of the arsenicals, the dangers of therapy are slight. Blood pressure recordings and urinary analyses should precede each injection. If the patient is toxic, treatment should be withheld. Contraindications to treatment based on constitutional diseases play but a small part. Rarely have we seen a pregnant luetic woman unable to tolerate treatment.

Meta-aminoparahydroxyphenylarsine oxide or mapharsen, developed by Tatum and Cooper, is being used exclusively in the two clinics. Two hundredths of a Gm. of mapharsen dissolved in 10 cc. of freshly distilled water is injected intravenously in the basilic or cephalic vein. In a week, if the previous injection was well tolerated, .04 Gm. of mapharsen is given. The third week it is increased to .06 Gm., which is the maximum weekly dosage. We believe mapharsen injections could be given more often than each week, and if we encounter a recent infection, showing either chancre

or rash, we would not hesitate to do so. In our clinic 1 cc. of 10 per cent bismuth salicylate dissolved in olive or peanut oil is injected intramuscularly into the gluteal muscle. It was decided about five years ago to give *both* the intravenous and intramuscular on the same visit. This method has proved satisfactory. During pregnancy there are neither courses nor rest periods. The dual therapy is given weekly from the time of diagnosis to the delivery of the child. We are not concerned with too much, but too little treatment.

The injection of protoplasmic poisons is, however, an operation and cannot safely be performed on all pregnant women by everyone.

Previous to the recent interest in syphilis, the incidence of fatalities due to arsphenamine therapy was low—probably no higher than deaths resulting from chloroform poisoning. Meirowsky, secretary to an investigating committee, reported one death in 13,000 injections of old salvarsan, and one death in 162,800 injections of neosalvarsan.

As the chemistry and pharmacology of the drugs have improved, the fatalities have decreased. In the United States, the National Institute of Health, at Washington, determines the total arsenical content, toxicity in white rats, and the trypanocidal activity of each lot of drug, and directs that minimum standards be met before the preparation can be placed on the market. This should have a beneficial effect.

REACTIONS

While there are several types of reactions from the arsphenamines, three are of particular interest:

1. The nitritoid reactions are not uncommon and are primarily of a vasomotor origin. Soon after an injection of arsphenamine, the face flushes. There is a sensation of heat, dyspnea or palpitation. The patient appears anxious. The pulse is weak and there is a drop in blood pressure. She prefers to lie flat. These signs and symptoms do not last long, and are relieved by adrenalin. Nausea and vomiting, particularly in those travelling by trolley car or subway, headache, dizziness and fever may occur and last several hours, forcing the patient to bed.

2. Arsenical dermatitis occurred in two of our cases previous to the use of mapharsen. Both women were colored. General itching is a warning to discontinue therapy, temporarily, at least. This lesion occurs early in treatment. In both cases, a generalized pyodermia was present. The eruption begins usually with a maculopapular or vesicular dermatitis, spreading over the entire body, face, trunk and extremities. In both cases, an intense edema was present. The patients appeared acutely ill. Exfoliation of the skin of the entire body occurs in about three weeks. Often an otitis media is present.

3. Hemorrhagic encephalitis occurs more frequently in pregnancy than in the nonpregnant woman. Cormia noted in forty-six women with this lesion that thirty-four were pregnant. It is a serious and often fatal complication following arsenical therapy. Ehrlich was familiar with this condition and believed it was not due to the drug but to some inherent weakness in the patient's blood vessels. It may also occur following an arsenical injection given intramuscularly. Since the damage is done early in treatment, usually under five and often following the second or third injection, it, apparently, is not an accumulation problem. The syndrome includes fever, headache, irritability, convulsions and coma. Death occurs in a day or two. The pathology is edema and multiple punctate or small ring-formed hemorrhages in the brain. Cormia reported a case in a pregnant woman in whom petechial brain hemorrhages were found not only in the mother but in the fetus as well. It is interesting that patients poisoned by inorganic arsenical compounds show large amounts of the drug in the brain but do not have an accompanying encephalitis.

DIAGNOSIS OF SYPHILIS IN THE NEWBORN

Whether a child born of a luetic mother should be subjected to treatment or await signs or symptoms of the infection is often difficult to decide. The problem becomes simpler if the following methods are considered:

1. *Examination of the Placenta.* The value of diagnosis of syphilis from the placenta has lost much of its former importance. When a mother and child are syphilitic, one would expect a placental infection. However, placental lues is uncommon. McCord diagnosed only forty-eight syphilitic placentas from 1,085 strongly positive luetic women. The late J. Whitridge Williams diagnosed the infection in 12.1 per cent of infants who were eventually non-syphilitic, and failed to diagnose the placental lesion in 20 per cent of children who were congenital syphilitics. Warthin believed that the spirochæta was more numerous in placentas of macerated fetuses than in those of syphilitic living children. A review of charts of luetic and non-luetic patients delivered on the same day at The Long Island College Hospital suggests that the difference in relative weights of the placenta to that of the baby is not reliable to help in the diagnosis of syphilis. Today, a pathologist hesitates to commit himself definitely unless the spirochæta is found.

2. *The Cord Wassermann Is Not Reliable.* A child with a positive cord serology may eventually be free of syphilis, and a newborn with a negative cord serology may eventually develop evidence of the infection. The positive cord serology may be the reagin of the mother passing the placental filter and not the true serology of the child. The maternal and cord blood should be taken at the same time and titers of their reagin compared. A strongly positive maternal serology and a negative or weakly positive one in the cord blood should give a brighter outlook, as the arsenical seems to be more spirochæticidal in the fetal than in maternal tissue.

3. *Dark field examination of the scrapings of the umbilical vein wall,* in a section taken near the placenta, offers promise. Ingraham found the spirochæta in nineteen out of twenty cases, but in sixteen syphilitic infants, the scrapings were negative. If the spirochæta is found, the diagnosis is proved. If, however, the organism is not seen, it should not be interpreted to mean that the child may not eventually develop the infection.

4. *Roentgen examination of the long bones* about the eighth day is probably the most reliable method of diagnosing congenital syphilis. Wegner described the pathology thirty-five years before Schaudinn discovered the spirochæta. McCord found osteochondritis in 51 per cent of 243 syphilitic fetuses at autopsy. McLean believed that the lesion is present practically always in congenital luetic children. *X*-ray diagnosis has been made of a syphilitic child in utero.

The pathology, an osteochondritis, takes place at the union of the epiphysis and diaphysis of the long bones—at Guérin's line. Normally, the line is straight and narrow, but in syphilis it is widened, wavy and opaque. Heavy metal deposits during prenatal treatment may confuse the picture.

5. *Pediatric Follow-up.* A child born of a syphilitic mother does best under the care of a pediatrician trained in syphilis therapy. The serology of the newborn is no more reliable than that of the cord. Repeated blood tests about four weeks following delivery should be done. If positive at this time, the child probably has the infection, and treatment is indicated. If negative, however, a repeated blood test is done every month for four months, and then every six months, until the child has reached the age of two.

SUMMARY

1. The researches of Schaudinn, Wassermann and Ehrlich should have accomplished much in preventing and treating syphilis in the pregnant woman.

2. Physical examination often fails to suggest syphilis in pregnancy.

3. Alteration of the covering of the chorionic villi, which takes place in the middle of pregnancy, may be responsible for the loss of protection during late pregnancy.

4. Spirochætal infection does not cause an early abortion.

5. Since syphilis, in practically all pregnant women, is masked or in the latent stage, the diagnosis must be made by a routine serological test.

6. Repeated late abortions, premature or full term stillbirths should arouse suspicion of syphilis.

7. Complement-fixation and flocculation tests should be done.

8. Provocative injection of 0.3 Gm. of arsphenamine may reactivate the reagin of the serum.

9. Injection of arsphenamine in non-syphilitic women does not cause a positive serology.

10. Spirochætae have been found in abortions and babies of women whose serology was negative to the Wassermann test.

11. Blood transfused from a luetic donor does not necessarily transmit syphilis.

12. Treatment is instituted primarily in the interest of the child. The maternal syphilis is secondary.

13. Arsphenamine is found in the fetus late in pregnancy; the placenta serves as a reservoir.

14. It is in the interest of the child to treat the mother in each pregnancy.

15. Pregnant women are subject to encephalitis more often than non-pregnant women.

16. Examination of the placenta for syphilis has lost much of its importance.

17. The cord Wassermann is not reliable.

18. Dark field scrapings from the umbilical vein wall offers promise.

19. Roentgen examination of the long bones is very valuable.

20. Pediatric follow-up of children born of luetic women is imperative.

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