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Original Article

The Possible Role of Intrauterine Infections in Unexplained Second Trimester Abortions and Macerated Stillbirths: A Study from a Single Center

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OBJECTIVE:

To investigate the role of intrauterine infections in unexplained second trimester abortions and stillbirths.

STUDY DESIGN:

Histopathologic and microbiologic evidence of intrauterine infection in the placentas, fetal membranes and fetal lung tissues of 18 unexplained second trimester abortions and macerated stillbirth cases as well as the placentas and fetal membranes of 10 healthy term neonates were investigated in a prospective study conducted in Ankara University School of Medicine, Turkey.

RESULTS:

Histopathologic chorioamnionitis and placental culture positivity rates in the study and control groups were 64.7 vs 0%. Bacteria were recovered from 90.9% of placentas and 36.4% of fetal lungs of the cases with histopathologic chorioamnionitis. Intrauterine infection was found in 66.7% of the whole study group, in 85.7% of the unexplained second trimester abortions, and in 54.5% of the macerated stillbirths.

CONCLUSION:

Intrauterine infection may be an important factor in unexplained stillbirths and second trimester abortions in centers where pregnancy follow-ups lack evaluation for asymptomatic infection.
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INTRODUCTION

Stillbirths are among the major determinants of the perinatal mortality rate, even in countries with low neonatal deaths. According to the current literature, the cause of stillbirths is unexplained in 12 to 59.2% of the cases, and the frequency of stillbirths due to clinically apparent intrauterine infection is only 2.4%.[1,2] Many second trimester abortions also remain unexplained.

Over the past two decades, much evidence has been collected suggesting that the inflammatory response of maternal and fetal tissues against intrauterine infections is the cause of stillbirths.[3–7] Severe intrauterine infections that occur during the early phase of gestation may also be the cause of second trimester abortions.[8–10]

In this 1-year prospective study, we investigated the role of intrauterine infection in unexplained macerated stillbirths and second trimester abortions.

MATERIALS AND METHODS

Control and study subjects were selected from the patients admitted to the Department of Gynecology and Obstetrics of Ankara University School of Medicine during the period between January 1st, 1999 and December 31st, 1999.

Cases of second trimester abortions consisted of spontaneous abortions between 12 and 22 gestational weeks calculated from the last menstrual date or of spontaneous abortions having weights less than 500 g or heights less than 25 cm. Cases of stillbirths consisted of intrauterine fetal deaths or fetuses with gestational age from 22 weeks till term or weight $\geq$500 g or height $\geq$25 cm that were born without a vital sign and did not give any response to 20 minutes of active resuscitation. Among the second trimester abortions and macerated stillbirths, cases lacking any lethal congenital malformations or maternal factors like uterine abnormalities, cervical insufficiency, trauma, hypertension, diabetes mellitus or any other chronic diseases that can lead to miscarriage or stillbirth were included in the study. The study group comprised a total of 18 cases. Seven of the study cases were second trimester abortions and 11 of them were macerated stillbirths.

Cases of control group consisted of vaginally delivered singleton neonates born consecutively to a stillbirth or second trimester abortion case that was assigned to the study, if and only if it was born within the same working shift of the same obstetricians and other health workers of the study group case, gestational age was

between 38 and 40 weeks, the birth weight was between 2500 and 4000 g, the apgar score at 5 minutes was ≥ 9 and the fetus was born from a mother without any history of hypertension, diabetes or any other chronic diseases. The control group comprised a total of 10 cases.

Families of all the cases were informed and specimens were collected after their written consent.

In order to detect intrauterine infection, specimens from placenta, fetal membranes, fetal lungs of the study group and specimens from placenta and fetal membranes of the control group were collected within 12 hours after delivery. Until specimen collection, fetuses of the study group and placenta and fetal membranes of all the cases were protected in clean storage boxes at $+4^{\circ}$C.

A questionnaire form was utilized to detect signs and symptoms of clinical chorioamnionitis, maternal urinary tract infection (UTI) during pregnancy and premature rupture of membranes (PROM). All of the mothers were interviewed and their hospital records were reviewed.

Specimen Collection

To avoid vaginal and peripheral contamination, surface sterilization of placentas was conducted with a solution including alcaliaminoalcaliglisin, ethanol, degluconate dechlorhexidine and allantoin (Manusprey®, Anios Laboratories, France). Surface sterilization of fetal skin was done with 10% polyvinylpyrolidone iodine solution. Equipments and gloves were replaced with new sterile ones after surface incision, before obtaining the tissues. Two cubic centimeters of deep placental and fetal lung tissues were obtained in sterile conditions and placed in separate sterile containers for microbiologic studies. Placenta and fetal membranes were placed in 10% formalin for delivery to the pathology laboratory.

Microbiologic Studies

Tissue samples were minced lightly in different containers using sterile equipment and were inoculated on media to isolate aerobic and anaerobic bacteria and fungus within 30 minutes of specimen collection. Blood agar, chocolate blood agar, eosin–methylene blue agar and sabouroud agar were used for culture growth. Inoculated media were kept for 5 days and controlled daily for bacterial growth. Bacterial identification was done with specific passages and dyes. After inoculation, the remaining tissues were frozen at -70°C in sterile containers for microbiological studies for genital mycoplasma and ureaplasma urealyticum. A commercial kit containing lyophilized liquid and agar media (Mycoplasma-Lyo®, Bio Merieux Sa 69280 Marcy l' etoile, France, Lot: 738427701) was used for the identification of genital mycoplasma and ureaplasma. All tissue inoculations in liquid media were carried out on the same day. Growth was controlled daily and detected with the change of color from yellow to pink. Then, passages were done to agar media and identification of the genital mycoplasma and ureaplasma urealyticum was performed according to colony morphology. The microbiologist who made the identification of microorganisms was blind to the cases during the study.

Histopathologic Studies

After macroscopic examination of the placental disc, fetal membranes and the umbilical cord, histopathologic examinations were conducted in three sections: fetal membrane roll taken from the placental margin, placental parenchyma including a vertical section of fetomaternal side of the placenta, and the umbilical cord section obtained from a distance of 4 cm proximal to the cord insertion to the placental disc. Histologic sections were stained with hematoxylin–eosin. Umblical cord stroma and vessels, amnion, chorion, chorionic vessels, chorionic plate, decidua, intervillous area and villi were examined for inflammation and other abnormalities.

Accumulation of a few acute inflammatory cells in the placenta and fetal membranes of healthy full-term babies born from asymptomatic mothers has been reported before. Based on other studies, histopathologic chorioamnionitis is defined as the presence of more than three polymorphonuclear leukocytes per high-power field in the fetal membrane sections.[6,7]

Statistical Methods

Results are given as mean $\pm$ standard deviation (mean $\pm$ SD) and rate (%). Groups are compared with Student's t-test, χ^2 tests and Fisher's-exact test using SPSS version 9.01 for Windows program and $p<0.05$ was accepted as statistical significance.

Ethical Approval and Financial Support

The study was approved by the Ethical Committee of Ankara University School of Medicine and funded by Ankara University Research Fund.

RESULTS

The total number of births in our center was 1621 in the year 1999. The total number of perinatal deaths was 40, and 10 (25%) of the cases were early neonatal deaths. In all, 24 (60%) of the perinatal death cases were macerated stillbirths, six (15%) were fresh stillbirths. Perinatal mortality rate, stillbirth rate, fresh stillbirth rate and macerated stillbirth rate were 24.7 per thousand, 18.5 per thousand, 3.7 per thousand and 14.8 per thousand, respectively.

The cause of death was undetectable in 12 (50%) of the 24 macerated stillbirth cases. Family consent could not be obtained for specimen collection in one case, and placenta and fetal membranes were lost during storage but the fetus was available in another case. A total of 11 cases of macerated stillbirths were

Table 1 Comparison of Maternal Age, Education, Employment Status, Maternal Gravidity and Parity of the Study and Control Groups

Groups	Maternal age (mean ± SD)	Maternal education ≤11 vs >11 years	Maternal employment status Working vs housewife	Gravidity Primigravide vs multigravide	Parity Primiparous vs multiparous	History of abortus or macerated stillbirth
Study ($n=18$)	29.6 ± 5.8	77.8% ($n=14$) 22.2% ($n=4$)	27.8% ($n=5$) 72.2% ($n=13$)	50% ($n=9$) 50% ($n=9$)	72.2% ($n=13$) 27.8% ($n=5$)	33.3 % ($n=6$)
Control ($n=10$)	25.7 ± 3.4	70% ($n=7$) 30% ($n=3$)	40% ($n=4$) 60% ($n=6$)	50% ($n=5$) 50% ($n=5$)	50% ($n=5$) 50% ($n=5$)	10% ($n=1$)
p-values	<0.05	>0.05	>0.05	>0.05	>0.05	>0.05

eligible for the study together with seven second trimester abortions without a detectable maternal and/or fetal cause. A total of 17 placentas and fetal membranes, 18 fetal lungs in the study group and 10 placentas and fetal membranes in the control group were eligible for evaluation.

All mothers in the study and control groups were Caucasian Turkish women. A comparison of maternal age, education, employment status, maternal gravidity and parity of the groups is demonstrated in Table 1. Mean maternal age of the study group and control group were 29.6 ± 5.8 and 25.7 ± 3.4 years, respectively. Education, employment status, gravidity and parity of the study and the control groups were statistically similar.

A comparison of the study and control groups with respect to the mean gestational age, birth weight, maternal UTI, clinical chorioamnionitis, PROM, histopathologic chorioamnionitis and bacterial growth rates during the current pregnancy is demonstrated in Table 2.

Mean gestational age and birth weight in the study group vs the control group were 24.3 ± 7.4 vs 39.4 ± 1 weeks and 900.9 ± 1026.1 vs 3411 ± 421.3 g, respectively. The statistically significant differences between gestational ages and birth weights of the groups were due to the selection properties.

The rate of maternal UTI in the study and the control groups were 27.8% ($n=5$) and 60% ($n=6$), respectively. The difference between the groups was not statistically significant.

Premature rupture of the membranes and clinical chorioamnionitis rates in the study group were 22.2% ($n=4$) and 16.7% ($n=3$), respectively. There was no history of PROM or clinical chorioamnionitis in the control group. The difference between the groups with respect to the rate of PROM and clinical chorioamnionitis was not statistically significant.

Histopathologic chorioamnionitis was diagnosed in 11 of 17 placentas (64.7%) of the study group and in none of the placentas of the control group. Histopathologic chorioamnionitis was significantly higher in the study group ($p<0.001$).

Bacteriologic growth was seen in 11 of 17 (64.7%) placenta tissues and in five of 18 (27.8%) fetal lung tissues of the study group. The 10 placentas that grew pathogens were also those diagnosed with histopathologic chorioamnionitis. In seven cases of the study group, although placenta cultures were positive, there was no bacterial growth in the fetal lung tissue. In four cases of the study group both the placenta and fetal lung cultures were positive for the same microorganism. In the case in which the placenta and fetal membranes were lost, bacterial growth was positive in the fetal lung tissue. There was no bacteriologic growth in the placentas and fetal membranes of the control group. The placenta tissue culture positivity was significantly higher in the study group ($p<0.001$).

Table 2 Signs and Symptoms of Maternal UTI, Clinical Chorioamnonitis (CCA) and Premature Rupture of Membranes (PROM), Histopathologic Chorioamnionitis (HPCA) and Bacterial Growth during the Current Pregnancy of the Study and Control Groups

	Study group ($n=18$)	Control group ($n=10$)	*p*-value
Gestational age (weeks)	24.3 ± 7.4	39.4 ± 1	<0.05*
Birth weight (g)	900.9 ± 1026.1	3411 ± 421.3	<0.05*
UTI (%)	27.8	60	>0.05†
CCA (%)	16.7	0	>0.05†
PROM (%)	22.2	0	>0.05†
HPCA (%)	64.7	0	<0.001†
Culture positivity (placenta) (%)	64.7	0	<0.001†
Culture positivity (fetal lung) (%)	27.8	0	

*By Student's *t*-test.
†By Fisher's exact test.

Bacteria isolated from cultures are listed in Table 3. None were anaerobic bacteria.

We also compared the cases with and without histopathologic chorioamnionitis in the study group (Table 4). In the subgroup with histopathologic chorioamnionitis ($n=11$), placenta and fetal lung culture positivity were 90.9% ($n=10$) and 36.4% ($n=4$), respectively. In the subgroup without histopathologic chorioamnionitis ($n=6$), bacterial growth was observed in only one placenta (16.7%) and none of the fetal lung tissue cultures.

Placental tissue culture positivity was significantly higher in the cases with histopathologic chorioamnionitis compared to the cases without chorioamnionitis ($p<0.05$). We accepted histopathologic chorioamnionitis and placental or fetal lung tissue culture positivity as a sign for intrauterine infection, and we assessed the rate of intrauterine infections in unexplained second trimester abortions and macerated stillbirths. Intrauterine infection was present in 66.7% (12/18) of the whole study group, in 85.7% (6/7) of the unexplained second trimester abortions and in 54.5% (6/11) of the macerated stillbirths. There were 11 placentas that were diagnosed as histopathologic chorioamnionitis, of which 10 grew pathogens in culture media, and there was one fetal lung that was culture positive in the study group. Of the 11 cases of macerated stillbirths, six were diagnosed as intrauterine infection based on the finding that in five of the cases histopathologic chorioamnionitis with bacterial growth in these placentas was present, and in one case bacteria grew in fetal lung tissue although placenta and fetal membranes of this case were lost during storage. Of the seven second trimester abortions, six were diagnosed as intrauterine infection based on the finding that in all of the cases histopathologic chorioamnionitis was present, although bacterial growth in placental tissues was observed in only five of these cases. Apart from the case whose placenta and fetal membranes were lacking, fetal lung culture positivity was observed in four additional cases. Of these four cases, two were macerated stillbirths and two were second trimester abortions. All four cases were already diagnosed as intrauterine infection due to histopathologic and microbiologic chorioamnionitis. The results are summarized in Table 5.

Table 3 Placenta and Fetal Lung Tissue Isolates

Isolate	Placenta	Fetal lung	Total
Ureaplasma urealyticum	2	1	3
Escherichia coli	2	1	3
Candida	2	0	2
Klebsiella species	1	1	2
Group B streptococci	1	1	2
Penicillium	1	1	2
α-Hemolytic streptococci	1	0	1
Gram(−) bacillus	1	0	1

DISCUSSION

Perinatal mortality in our center is still high, and macerated stillbirths are the major determinant of our perinatal mortality. It was previously reported that the etiology is unknown in 12 to 59.2% of the stillbirths.[1,2] Macerated stillbirth with no detectable etiology is a major problem in our center. Histologic chorioamnionitis has been reported to exist at a rate of 5 to 30% in term deliveries. This incidence is higher in developing countries. Folgosa et al.[4] reported the incidence as 67% in their study in Mozambique. Moyo et al.[11] reported it as 30% in their study in Zimbabwe. Accumulation of inflammatory cells in normal term deliveries is thought to occur during the period between rupture of the fetal membranes and the delivery.[4,6] In our study, we did not observe any accumulation of inflammatory cells in normal term deliveries of the control group. This may be due to the strict sanitary conditions in our tertiary health center and absence of history of premature rupture of

Table 4 Comparison of Bacterial Growth in Tissues and Fetal Lung Infection Rate between Histopathologic Chorioamnionitis Positive and Negative Cases in the Study Group

Study group	Histopathologic chorioamnionitis (+) cases ($n=11$)	Histopathologic chorioamnionitis (−) cases ($n=6$)	p-value
Culture positivity (placenta)	90.9% ($n=10$)	16.7% ($n=1$)	<0. 05*
Culture positivity (fetal lung)	36.4% ($n=4$)	0% ($n=0$)	>0.05*

*By Fisher's-exact test.

Table 5 Rate of Intrauterine Infections in Unexplained Second Trimester Abortions and Macerated Stillbirths

	Second trimester abortions ($n=7$)	Macerated stillbirths ($n=11$)	Study group (total) ($n=18$)	Control group ($n=10$)
Intrauterine infection (n)	85.7% (6)	54.5% (6)	66.7% (12)	0% (0)

Table 6 Summary of Selected Prior Studies Reporting Various Outcomes and a Summary of Some Outcomes of the Present Study

Author	Study population	Premature rupture of membranes (%)	Clinical chorioamnionitis (%)	Histopathologic chorioamnionitis (HPCA) (%)	Bacterial recovery from placenta (%)	Bacterial recovery from fetal tissue (%)	Bacterial recovery from placenta and/or fetal tissue/other fetal specimens (%)	Bacterial recovery from placenta and/or fetal tissue/other fetal specimens in histopathologic chorioamnionitis (+) cases (%)
Quinn et al. (1987)	Study group — 33 perinatal deaths (stillbirths+deaths within 48 hours after delivery, cases with congenital anomalies included) vs	—	26	57,6	72,7	—	—	71.4% of all HPCA (+) cases of the study and control groups
	control group — 20 term alive newborns		0	5	10			
Zlatnik et al. (1990)	95 preterm deliveries	56	21	54	40	—	—	68
	16–34 weeks gestation ($n = 50$)			72				54
	27–34 weeks gestation ($n = 45$)			33				92
Moyo et al. (1996)	Study group — 66 stillbirths vs	—	—	79	27	41	65	55
	control group — 66 term alive newborns			30	4,5		59	18
Folgosa et al. (1997)	Study group-58 stillbirths vs	—	30	96	28	—	71	68
	control group — 58 term alive newborns		8	67	28		43	35
Mc Donald et al. (2000)	129 mid-gestational spontaneous abortions or stillbirths (16 – 26 weeks gestation)	53	30	69	57	49	66	81
Tolockiene et al. (2001)	Study group — 117 stillbirths vs	—	—	82	41,7	27,6	51	50
	control group — 126 term alive newborns			68	27			37
Present study	Study group — 18 second trimester spontaneous abortions or stillbirths vs	22,2	16,7	64,7	64,7	27, 8	90, 9	90, 9
	control group — 10 term alive newborns	0	0	0	0	Not studied	0	No HPCA

membranes or clinical chorioamnionitis in the control cases. We suggest that, in normal healthy pregnancies, if the environment is sterile, accumulation of inflammatory cells or bacterial contamination of placenta and fetal membranes do not occur in a normal birth process during the time between the rupture of the membranes and the delivery.

Chorioamnionitis is the most common histopathologic finding in the placentas of perinatal deaths and macerated stillbirths. In many different studies the rate of histopathologic chorioamnionitis was reported as 54 to 96% in study groups composed of perinatal deaths or macerated stillbirths. In these studies, the rate of histopathologic chorioamnionitis was reported to be 5 to 68% in control groups composed of healthy offspring.[4,6,11–13] Quinn et al.[6] had reported histopathologic chorioamnionitis to exist in 70.8% of the perinatal mortality cases with no morphologic cause and in 22.2% of the cases with a defined cause of death. Zlatnik et al.[7] reported histopathologic chorioamnionitis in 72% of the second trimester preterm deliveries and in 33% of the third trimester preterm deliveries. In our study, although the rates of PROM, clinical chorioamnionitis, maternal UTI rate were not statistically different between the study and control groups, histopathologic chorioamnionitis was significantly higher in the study group than the controls.

In most of the previous studies, high bacterial growth rate in the placental tissue cultures in the study groups vs controls has been accepted as the evidence for intrauterine infection to be a major cause of fetal death. Quinn et al.[6] reported a bacterial growth rate of 71.4% in the placental cultures of the cases with histopathologic chorioamnionitis and a bacterial growth rate of 10% in their control group. In macerated stillbirths, the rate of bacterial growth in placentas with histopathologic chorioamnionitis was reported to be 40 to 88%, while it was 15 to 45% in cases without histopathologic chorioamnionitis.[4,6,11,13] Tolockiene et al.[13] reported that the risk for stillbirth was doubled if both inflammation and bacteria were present. Zlatnik et al.[7] reported bacterial growth in 92% of third trimester preterm deliveries and in 54% of second trimester preterm deliveries with histopathologic chorioamnionitis and suggested that histopathologic chorioamnionitis was not synonymous with infection, in the second trimester. McDonalds and Chambers[10] reported microorganism recovery in 57% of the placentas and 49% of the fetuses in midgestation abortions, and in their study the rate of histopathological chorioamnionitis was 81% among cases with culture positivity. In all of the previous studies, a high incidence of bacterial growth has been demonstrated in cases with histopathologic chorioamnionitis. Both the presence of histopathologic chorioamnionitis and bacterial growth rates seem to increase with gestational age in these studies and quantitative differences in their results may be related to study designs. Various outcomes of selected prior studies are summarized in Table 6.

Because of the strict sterility rules to avoid contamination in our method and absence of lactobacillus growth of the normal vaginal flora in the species collected, we believe that our high bacterial growth rate represents true infection. Taking the high incidence of bacterial growth in histopathologic chorioamnionitis positive cases of our study group into account, we suggest that histopathologic chorioamnionitis could be considered synonymous with intrauterine infection.

Although there was no statistical difference with respect to the presence of clinical chorioamnionitis, PROM or maternal UTI between the groups, the species of the bacteria recovered from placentas and fetal lung tissues of the study group cases were predominantly enteropathogens. Thus, we suggest that bacterial invasion can occur through intact membranes in an ascending way, and we think that asymptomatic anogenital colonization may play a role in the development of intrauterine infections.

Goncalves et al.[14] reported that the earlier the gestational age at delivery, the higher the frequency of intra-amniotic infection was in preterm deliveries.

The statistically significant presence of histopathologic chorioamnionitis, placental tissue culture positivity, high incidence of bacterial growth in placentas and in tissues that should theoretically be sterile, and fetal lung infection in the group with histopathologic chorioamnionitis in our study group may demonstrate the possible role of intrauterine infection in unexplained second trimester abortions and macerated stillbirths.

It seems that the earlier the intra-amniotic infection, the worse the fetal outcome and severity of the intrauterine infection, which plays an important role in the outcome of the pregnancy. Severe intrauterine infection during the early phase of gestation may most probably cause a second trimester abortion.

This was a 1-year study conducted in a single center. The size of the study group was small due to the selection of the cases among only 1621 annual births. We believe that, this study provides additional evidence for ''hidden'' intrauterine infection in second trimester abortions and macerated stillbirths without a clinical definitive cause.

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