The Vinyl Institute

TECHNICAL INFORMATION

POTENTIAL EFFECTS OF VINYL CHLORIDE ON HUMAN OFFSPRING

Prepared by

THE VINYL INSTITUTE

Medical Subcommittee of the Technical Committee

This info is for PVC plants not compounding plants.
PVC plants use pure VCM to make PVC powder.
Exposure potential is far greater in these plants than at Gallman.
OSHA action level

Tulane + CDC - study
LA + Neg. mice images from the USA

ISSUED: DECEMBER 1987

POTENTIAL EFFECTS OF VINYL CHLORIDE ON HUMAN OFFSPRING

SUMMARY

Vinyl chloride monomer (VCM) is one of the most intensely studied chemicals that is used in industry today. Although it is a known human and animal carcinogen, many other alleged health concerns are not supported by animal or human data. Early or preliminary studies of offspring by some investigators have suggested that VCM causes birth defects and miscarriages. However, critical peer review and subsequent research have shown that there is no basis for such fears.

What we do know from decades of research on VCM is that studies with pregnant animals have shown that VCM can undergo placental transfer and, at high levels, cause cancer in their offspring. Other animal studies have indicated that VCM does not produce any mutations in subsequent generations.

Furthermore, numerous animal and human studies have shown that VCM does not cause birth defects or reproductive effects. While some human studies have claimed that VCM causes birth defects and miscarriages, close examination by numerous experts have found these early reports to be seriously flawed and not supportive of an effect.

Transplacental Carcinogenicity

The carcinogenic potential of VCM is well recognized. Many studies have shown that it causes cancer in a number of different animal species and conditions (Viola et al., 1971; Maltoni and Mehlman, 1984; Keplinger et al., 1975). The fact that VCM causes angiosarcoma in man is evidenced by numerous studies (Creech and Johnson, 1974; Delorme and Theriault, 1978; Fox and Collier, 1977; Noria et al., 1976). Studies by Maltoni (1974) and Maltoni and Mehlman (1984) also have shown that VCM is transplacental carcinogen. When pregnant rats were exposed to high levels of VCM, an increased incidence of cancer was observed in the offspring.

Animal Studies of Developmental and Reproductive Effects

The exposure of males and/or females to toxic chemicals prior to or following conception may provide an opportunity for

deleterious effects to occur. Because VCM has been found to cause mutation in some non-reproductive cells (Bartsch et al., 1976); McCann et al., 1975; Rannug, 1974; Drevon and Kuroki, 1979; Basler and Rohrborn, 1980), studies have been conducted to determine whether VCM can cause mutations in germ cells (egg, sperm) that could effect viability or produce body anomalies.

In 1976, Anderson et al. examined VC mutagenicity in fertile male mice using the Dominant Lethal Assay. These investigations exposed mice to VC for 6 hours per day for 5 days in concentrations of 3,000, 10,000 and 30,000 ppm. To assure that their test system was functional, this study employed two known mutagens as positive controls (cyclophosphamide and ethyl methane sulphonate). No mutagenic effects were observed with VCM at any stage of spermatogenesis while dominant lethal effects were observed with the positive controls.

This early work of Anderson et al. (1976) was later confirmed by Himeno et al. (1983) in a dominant lethal study using two different exposure conditions. One group of CD-1 mice was exposed for four hours per day during five consecutive days to 10,000 ppm of VC, and the second group of mice was exposed four hours per day, five days per week over a 10 week period to 5,000 ppm VC. Again, no dominant lethal mutations were observed following VC exposure.

Using another approach, Peter and Ungvary (1980) studied the germinal mutation potential of VCM in the mammalian spot test. Following the mating of inbred females with rotated-bred males, they exposed groups of females on the 10th day of pregnancy to 0 or 4,600 ppm of VCM for 5 hours or to cyclophosphamide, the positive control. Cyclophosphamide caused a significant increase in the number of white or colored spots, while VCM did not cause an increase in color spots. Also, there was no effect on litter size at birth or at the end of the 3-5 week observation period. The authors concluded that although gene mutation had been reported in fruit flies exposed to VCM, there is no evidence that VCM causes mutations in mammals.

Other studies have focused on the potential effects of maternally inhaled VCM on embryonal and fetal development. In studies by John et al. (1977 and 1981) groups of rats and rabbits were exposed to 0, 50, 500 or 2,500 ppm VC for 7 hours per day during the critical development phase (organogenesis) for each species (days 6 to 15 for mice/rats and days 6 to 18 for rabbits). Additional groups of pregnant females were simultaneously exposed to VCM (2,500 ppm for rats and rabbits and 50 and 500 ppm for mice) plus 15% ethanol in their drinking water over the same period. Ethanol, a known reproductive toxin, was used because it is known to block the primary metabolic pathway for VCM. Although high levels of VCM caused

frank maternal toxicity, no significant embryonal toxicity, fetal toxicity or teratogenic effects were observed. Greater maternal embryonal and fetal toxicity but not teratogenic effects were observed following exposure to ethanol and VCM. Because of the limited control data which was provided, it could not be determined whether this increase in toxic response was largely due to ethanol alone or the inhibition of VCM metabolism (detoxification) of VCM. However, these studies have further underscored the concerns associated with ethanol consumption during pregnancy.

Ugvary et al. (1978) also carried out a detailed study in rats of the potential of VCM to cause birth defects. In their initial experiments, they exposed females on the 18th day of pregnancy to either 2,000, 7,000 or 12,000 ppm VCM for 2.5 hours. Analyses of the maternal blood, amniotic fluid, and fetal tissue demonstrated that VCM could be transferred across the placental barrier from the mother to the fetus. In subsequent experiments they exposed females to 1,500 ppm VCM 24 hours per day over three different periods of their pregnancy and looked for fetal effects. No birth defects occurred as the result of VCM exposure. Fetal toxicity was evident in only one of the three groups.

All of these studies cited above are remarkable in two ways. First, the exposure levels used in these experiments are for the most part several orders of magnitude above levels of VCM in the workplace and many orders of magnitude above that in the community. Such exposure would only be encountered under rare, catastrophic situations and would likely be short-lived relative to these studies. Secondly, even though the females were exposed to very high levels of VCM, the evidence indicates that VCM does not cause dominant lethal mutations or birth defects. Furthermore, these data indicate that the levels of VCM in the workplace and the ambient air are not of concern to the mother, embryo or developing fetus.

Human Studies of Mutagenic, Developmental and Reproductive Effects

Numerous studies of human populations have been conducted to evaluate the potential of VCM to cause birth defects or other reproductive effects. The studies in humans have been carried out with workers employed in polyvinyl chloride (PVC) production or fabrication facilities, and other studies have examined communities in which a PVC production or fabrication facility is located. In contrast to the well controlled conditions of the animal studies in the laboratory, these human studies have had to contend with many confounding factors such as smoking, alcohol, maternal age, maternal infections, lack of exposure information, etc. The ability or inability of the author to deal with these variables has frequently affected the utility of the study and the validity of the authors' conclusions. Many of these problems have been encountered in studies of the effects of VCM on human reproductive outcome.

One of the earliest studies of the potential of VCM to influence human reproductive outcome was conducted by Infante et al. (1976a). Fetal loss among wives of VCM exposed workers was studied by interviewing husbands employed in VCM polymerization and PVC fabrication facilities in Ohio. No interviews were conducted with wives and no maternal age information was obtained. Among the workers potentially exposed to VCM, fetal loss was observed to be 15.8% compared to 8.8% among the unexposed controls. This effect was observed in men younger than 30 years old.

The above study by Infante et al. (1976a) has been reviewed by a number of investigators and has been found to be inadequate and misleading (Stallones, 1987; Clemmensen, 1982; Haas and Schottenfeld, 1979). This credibility and validity of the conclusions from this survey have been imposed by the absence of maternal interviews and information on maternal age, smoking or alcohol consumption and inappropriate statistical treatment of the data. Furthermore, it was presumed that all workers had a significant exposure to VCM.

In addition to the above problems, Paddle (1977) asked for clarification of the age adjustment procedure used by Infante et al. (1976a). The response given by Infante et al. (1976b) tried to explain the age adjustment procedure, but the response also revealed that there were four different age-based categories in the original study. The alleged effect upon fetal loss could only be detected in the 25-29 year old age group. Such a specific response is hard to explain on any basis since one normally expects the overall incidence in fetal defects to increase with increasing observation for the presumed effect in the 25-29 year age group by pointing out that the fetal loss in the unexposed group was substantially lower than for any other age group within the unexposed population. The conclusion of Stallones was that the study was seriously flawed by the lack of internal consistency, and the study should be discarded on that basis alone.

A recent study was conducted by Lindbohm et al. (1985) which examined spontaneous abortions among women employed in the plastics industry. The study was conducted in Finland during the years of 1973 to 1980 on workers who belonged to the Union of Chemical Workers, and whose potential exposure were to a variety of plastics materials including VC, styrenes, butadienes, acrylonitriles, and polyurethanes. Cases were selected from women who had been union members during their first trimester of pregnancy, and selections were done so that a given case was primarily exposed to only one type of plastic or monomer. Controls were selected from women not having a spontaneous abortion. Exposure (yes or no only, no quantitation) was determined by having the physicians who treated a given patient fill out a questionnaire.

When the data from Lindbohm et al. (1985) was examined, no difference in the rate of spontaneous abortions could be determined between the case and control populations for women working with PVC or PVC thermal degradation products. Although the number of women in the study was low, the statistical power of this study was sufficient to detect a two-fold increase in fetal wastage. Therefore, this study indicated that there was no association between VCM exposure and the occurrence of spontaneous abortion.

In addition to these studies of workers, a number of investigators have examined the occurrence of birth defects in communities surrounding plants which use VCM to make PVC. Infante (1976) has published a study of birth defects in a number of communities in Ohio which contained PVC production facilities. He has reported that the rate of birth defects in the communities producing PVC was greater than in neighboring communities that did not produce PVC.

One obvious problem with this Infante study was the total lack of any quantitative exposure data as in his previous study. Besides the lack of exposure data, no effort was made to correlate the rate of defects with distance from production facilities. If the defects were correlated with VC exposure, then one might expect a greater frequency of birth defects closer to the production sites with lower frequencies away from a given facility. When Edmonds (1976) examined the Infante data as frequency of defects vs. distance from a given facility, he could find no difference between the exposed and unexposed populations, and that observation weakens any putative link between observed birth defects and VC exposure.

Bias is a major concern in the Infante (1976) study because of the way he examined and combined populations for analysis. There are three communities in the study which contained PVC plants, and those cities are Painesville, Ashtabula, and Avon Lake. For comparison communities without PVC plants, 10 cities were chosen for their proximity to the exposed communities. Of the 10 control communities, two of them (Geneva and North Ridgeville) had higher malformation rates than the exposed communities containing PVC facilities. Since North Ridgeville was proximate to Avon Lake, according to Infante, the North Ridgeville data were combined with data from Painesville, Ashtabula, and Avon Lake even though it did not contain any VC operations within its boundary. This combination of data made a more striking difference between the exposed and unexposed groups whereas the difference would have been diminished if North Ridgeville was properly placed with the unexposed data. This gerrymandering in the case of North Ridgeville is of particular concern since it is 10 miles from the nearest plant and since its southwest location is not in the line of typical prevailing winds.

Another point to examine in the Infante study is the question of the CNS defects compared to the control population. Edmonds' (1976) examination of the data could not find an association between VC exposure and reported CNS defects. Edmonds also believes that localized increases can occur sporadically, but these localized increases do not always signal a potential problem. Moreover, Oakley (1981) examined CNS defects nationwide as part of an ongoing activity of the Center for Disease Control (CDC). Oakley found that the frequency of CNS defects has been decreasing in all regions of the country at a steady rate, and the decrease has been occurring since the 1930's.

Since CNS defects were a major concern of the Infante study, Edmonds et al. (1978) examined the presumed relationship of this defect to VC exposure in offspring of Hanawha County, West Virginia residents. In contrast to Infante et al. (1976a) and Infante (1976), Edmonds examined geographic distribution of CNS malformations in relationship to the PVC plant and attempted to quantitate ambient VC levels in the community. When Edmonds examined the malformation rates from matched pairs of exposed and unexposed residents, he could find no correlation with distance from the plant site. He did find some suggestive patterns in which more exposed were northeast and more unexposed south of the plant, but the correlation did not remain when wind and particulate deposition patterns were examined. VC was measured in the community after one large release, and levels of 0.1 to 0.2 ppm VC were found in grab samples to the northeast of the plant site. He was also able to determine emission data during his study period (1970-1974). He found that the rate of CNS malformations was declining during the study period, and the decline in CNS defects preceded the decrease in VCM emissions from the plant sites by about nine months. Edmonds concluded from his study that he could not find any correlation between any wind-borne pollutants and the incidence of CNS defects in Kanawha County, West Virginia.

Theriault et al. (1981 and 1983) also examined the presumed relationship of community VC exposure and the appearance of a variety of birth defects. Their study was conducted in Shawinigan, Canada during the period of 1966 to 1979. In addition to examining the geographic distribution of defects and attempting to quantitate ambient VC levels in the air like Edmonds et al. (1978), this study also examined the seasonal variations in VC levels and malformation rates.

Geographic distribution of malformation rates were examined in Shawinigan and comparison communities by using school district boundaries. The rate of defects was constant for each school district in Shawinigan as well as the comparison areas, and the ratio of observed to expected defects was always close to one (1). The ratio of observed to expected defects was approximately one (1) for the school district with the PVC plant as well. Further comparisons were made between school districts

with high and low VC levels, and no correlation could be found between the exposed and unexposed groups for CNS or any of the other malformations. One group, however, did show an increase in malformation rates, but it was located furthest from the plant and would have had the lowest degree of exposure. Consequently, no association was found between the geographic distribution of malformations and VCM exposure.

Although Theriault et al. (1983) reported that seasonal variations in birth defects corresponded with variations in atmospheric concentration, they concluded that a causal association between VCM and birth defects was not supportable. VCM concentration did not correlate with the distribution of birth defects and malformation rates were not high near the plant or in areas where VCM levels were the highest. Furthermore, districts with the highest rates were farthest from the plant.

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RECEIVED

JUN 12 1991

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Dear Ms. Jones:

As per our conversion I am forwarding to you one copy of the St. Gabriel report dated September 27, 1989. Please, call if you should need any additional assistance.

Dianne Dugas/df
Dianne Dugas
Office Chief

GGC 000793

Rec'd 5-1 retu d

Final Report

St. Gabriel Miscarriage Investigation East Bank of Iberville Parish, Louisiana

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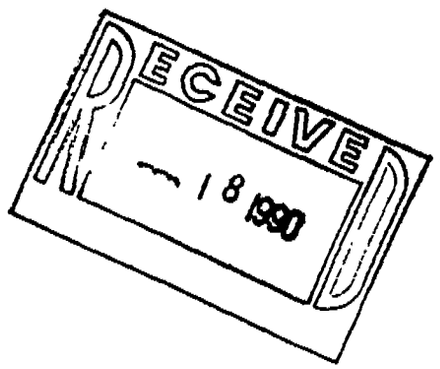
For

Louisiana Department of Health and Hospitals
Baton Rouge, Louisiana 70821

September 27, 1989



This study was supported by funds from the Comprehensive Environmental Response, Compensation and Liability Act trust fund, by Interagency Agreement with the Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Department of Health and Human Services.

FINAL REPORT

ST. GABRIEL MISCARRIAGE INVESTIGATION

EAST BANK OF IBERVILLE PARISH, LOUISIANA

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September 27, 1989

This study was supported by funds from the Comprehensive Environmental Response, Compensation and Liability Act trust fund, by Interagency Agreement with the Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Department of Health and Human Services.

ABSTRACT

In early 1987, the residents of St. Gabriel, Louisiana, expressed concern over what they perceived to be an elevated rate of miscarriage in their community and a possible relationship to air contaminants. Tulane University School of Public Health and Tropical Medicine conducted an investigation to determine if the rates of miscarriage and stillbirth were in excess of those expected on the basis of historical records or results of other studies of fetal loss.

Women between the ages of 18 and 50 at the time of the study, who had conceived between April 1, 1982, and April 1, 1987, and had delivered between May 1, 1982, and December 31, 1987, while residents of the east bank of Iberville Parish, were included in the study.

Multiple methods of case ascertainment were employed. Volunteers among those screened were recruited by public notification, telephone survey, mail notification and community outreach. Non-volunteers were identified from hospital records, emergency room logs and vital records. With all methods of ascertainment, 372 live births, 7 stillbirths and 69 miscarriages were identified among 354 women. Of 69 miscarriages identified, 54 were considered documented. For a miscarriage to be considered documented, medical records had to indicate a pregnancy with no subsequent live birth or the medical records of a hospital, physician or other health care provider had to indicate a fetal loss.

The documented miscarriage rate was 12.7% $\pm$ 1.6%, and the miscarriage rate using both documented and undocumented miscarriages was 15.7% $\pm$ 1.7%. Miscarriages among white women are relatively well ascertained, and the rate is not statistically significantly higher than expected, given the age structure of the pregnant white women. The observed age-specific rates for single pregnancies do not exceed the rates found in several comparable historical studies. Miscarriage rates for blacks are lower than rates for whites, but miscarriages among blacks are less well ascertained, and a firm conclusion cannot be drawn on the basis of available data. However, the observed miscarriage rate for blacks is consistent with rates found in studies with similar ascertainment. The age-adjusted miscarriage rates are below the levels set out in the protocol as being elevated.

Stillbirth ratios are based on very small numbers and are not statistically different from those for the entire State.

On the basis of analysis of these data and criteria established before the investigation, the rates found were judged not to be elevated and further study c miscarriages in the area is felt not to be warranted at this time. We recommend 1) that study results be communicated to the residents in a series of meetings, with ample time for questions; 2) that women consult with their health care providers for information on the risk of fetal loss with increasing maternal age; 3) that a model protocol for the investigation of miscarriage be designed so that results of studies from different areas can be compared, and 4) that guidelines for assessing the results of such surveys be developed.

EXECUTIVE SUMMARY

Background

In early 1987, the residents of St. Gabriel, Louisiana, express d concern over what they perceived to be an elevated rate of miscarriage in their community and a possible relationship to air contaminants. The Louisiana Department of Health and Hospitals requested that Tulane University School of Public Health and Tropical Medicine conduct an investigation to determine the rates of miscarriage and stillbirth in the area. The Agency for Toxic Substances and Disease Registry provided funding for the study and the Centers for Disease Control provided technical assistance.

Objectives and Criteria for Evaluation

The objectives of the study were to determine the rates of miscarriage and stillbirth on the east bank of Iberville Parish, Louisiana (including the towns of St. Gabriel, Sunshine and Carville) and to determine if the rates were in excess of those expected on the basis of historical records or the results of other studies of fetal loss. The study was not designed to address the impact of environmental contaminants or environmental exposures upon fetal loss.

As part of the protocol, criteria were established before the study for the evaluation of the results. These criteria were that a miscarriage rate of <15% would be considered within the expected range, a rate of 15%-24% would requir further analysis of known risk factors, with the Technical Advisory Committee judging whether the adjusted rate was elevated, and a rate of ≥25% would require further investigation.

Case Definition and Study Methods

Women between the ages of 18 and 50 at the time of the study who had a pregnancy ending between January 1,1982, and December 31, 1987, while a resident of the east bank of Iberville Parish, were recruited for this study. For the study analysis, all pregnancies conceived between April 1, 1982, and April 1, 1987, and delivered between May 1, 1982, and December 31, 1987, in the study area were included. Pregnancies which resulted in live birth, miscarriage or stillbirth were included in the study.

Multiple methods of case ascertainment of pregnancy were employed. Volunteers for the study were obtained by several methods, including public notification, telephone screening and mail notification. Those who volunteered for the study were screened for age and residence, and those found to be eligible were interviewed. Interviewers obtained a fertility history, descriptive information on residence and occupation, selected medical information, and information on smoking and alcohol consumption.

Hospital records, emergency room logs and vital records were reviewed to identify pregnancy outcomes of women who did not volunteer (non-volunteers). A limited amount of descriptive information was obtained from these sources -- for example, maternal age, race, education and partial fertility history.

Case Ascertainment

Public notification included the use of print, radio and television media to publicize the study. Flyers and bulletins were distributed throughout the area, including distribution to groups such as the PTA, miscarriage support group and church congregations. Letters to physicians and other health care providers apprised them of the study and requested them to notify patients who might be eligible. A 24-hour toll-free hot line was established to answer questions and to allow women to volunteer for the study. The hot line received 117 calls -- 36 for information only and 81 from women volunteering for the study. These 81 women were screened for eligibility, and the 61 found to be eligible were interviewed.

After the intensive public notification efforts, a telephone screening survey was conducted to locate women eligible for the study. Bu using the 1987 telephone list and an updated list of 1988 phone numbers from the phone company, each household with a phone in the community was contacted. In the attempt to reach a number, up to 25 calls were placed at various times throughout the day and evening. Women who had responded by another method (mail (see below) or hot line) were not recontacted. Of the 1,085 residential telephone numbers, women at 129 had already responded to other recruitment efforts. Of the remaining 956 numbers, 63 were disconnected (7%). Of the remaining 893, 877 were contacted and 16 could not be reached. Of the 877 women contacted, 858 were screened for eligibility, and 19 refused screening. Of those screened, 739 reported being ineligible for the study, and 119 (14%) were eligible and interviewed.

To encourage participation in the study and to inform women who did not have phones, notices were mailed to all residents identified from the post office rolls. Three follow-up mailings were sent to addresses from which no one had responded to other means of solicitation. Each mailing contained a return postcard. The total number of residential addresses in the study area was 1,163. From these, responses were received from 290 households (25%): 182 had been identified by other methods, and the other 108 were screened for eligibility. Seventeen were found to be eligible and not already participating in the study. Of these, 14 (82%) were interviewed and 3 refused.

We reviewed vital records to identify live births meeting study criteria for maternal age, residence and time period. This allowed us to ascertain live births not found through interviews and provided a means for checking the

degree of case ascertainment of live births among the volunteers. Vital records showed 169 live births to 145 women who met study criteria but who had not volunteered. Forty-two percent of all women with eligible live births had not volunteered. This included 50% of black women versus 31% of white women, and 52% of women under 30 years of age versus 27% of women 30 years of age and older. These non-volunteer women were not from any particular residential location. Various community outreach attempts were made to include these women in the study. Following these efforts, an additional 10 women responded; 6 were found to be eligible and were interviewed. As established in the protocol, direct follow-up of women identified from vital records was not permitted. However, sociodemographic data and partial fertility records were constructed from vital records data for these non-volunteer women.

An independent search of hospital records and emergency room logbooks was conducted to identify adverse pregnancy outcomes that met study criteria. This search was intended to identify pregnancy losses among women who had moved from the study area or who had not volunteered for the study. Using vital records, we identified nine hospitals in which over 99% of women in the area delivered. The records of all 9 hospitals were reviewed, and an additional 12 miscarriages were identified. Three of these women, when contacted by the hospital, agreed to be interviewed.

Results

By using all methods of ascertainment 372 live births, 7 stillbirths and 69 miscarriages were identified among 354 women. The 372 live births were identified to a total of 345 women, 203 births to 200 volunteer interviewed women, and 169 births to 145 non-volunteer women found through vital records only. Sixty-nine miscarriages were found, including 57 from volunteer women and 12 from non-volunteers who were found on hospital record review. Seven stillbirths were ascertained.

Criteria for documenting a pregnancy outcome were established before the study as part of the protocol. For a miscarriage to be considered documented, medical records had to indicate a pregnancy with no subsequent live birth or the medical records of a hospital, physician or other health care provider had to indicate a fetal loss. Of the 69 miscarriages identified, 54 were considered documented. Undocumented miscarriages included those for which records from the health care provider could not be obtained (1), a medical condition other than miscarriage was recorded (4), no medical care was sought (5), or medical release consent forms were not returned (5). Of 7 stillbirths, 6 were documented.

The overall documented miscarriage rate was 12.7% (54/426) $\pm$ 1.6%. The study criteria call for miscarriages to be documented if they are to be

included in the study. However, miscarriages that could not be documented were reported. The rate of miscarriage using both documented and undocumented miscarriages was 15.7% (69/441) ± 1.8%.

The documented miscarriage rate for whites, 17.4% (32/184) ± 2.8%, is higher than that for blacks, 9.2% (22/240) ± 1.9%. Reasons for the difference between these rates include 1) better ascertainment of pregnancies (68% volunteered among whites versus 48% among blacks), 2) more complete documentation of reported miscarriages (89% among whites versus 67% among blacks), 3) earlier ascertainment (30% before 8 weeks gestational age of pregnancy among whites versus 12% before 8 weeks among blacks), and 4) older age of white mothers (32% 30 years and older versus 23% 30 years and older among black women). When the white documented miscarriage rate is adjusted to the age distribution of th black population, the white miscarriage rate decreases to 15.1% ± 2.7%.

A woman who has had a prior miscarriage is at greater risk of having a miscarriage in subsequent pregnancies than a woman without prior fetal loss. Thus, pregnancy outcomes for a specific woman are not independent events. In addition to the miscarriage rate based on all pregnancies in the study period, two additional miscarriage rates were examined, one based on the first study pregnancy to a woman and the other based on a single, randomly selected study pregnancy. The two rates for documented, white, age-specific miscarriages based on a single pregnancy (either the first or a random pregnancy) were compared with rates obtained in several prospective and one retrospective study of single pregnancies. When these rates were compared, no significant increase in the white miscarriage rates was found, except in the case of a study that seemed to have less complete ascertainment of miscarriages than the current study.

Documented miscarriage rates for blacks were lower than rates for whites, probably for the reasons previously discussed, including a lower rate of volunteers, later gestational age and less frequent documentation of miscarriages among black women. Because of the possibility of underascertainment of miscarriages among blacks, no firm conclusions can be drawn about rates among blacks. However, the age-adjusted, documented black miscarriage rate for a single random study pregnancy (11.4%) is comparable to the rate (10.9%) found in a prospective study of single pregnancies with similar low ascertainment of early miscarriages (15% of miscarriages <8 weeks gestation). The black miscarriage rate for documented and undocumented pregnancies combined (15.7%) is also similar to the 14.6% rate found in a retrospective study of documented and undocumented single black miscarriages.

Documented study stillbirth ratios of 6.6 per 1000 (1/152) among whites and 22.9 per 1000 (5/218) among blacks were found. White ratios are comparable to those for all whites in Louisiana (6.4 per 1000). The observed black stillbirth ratio is not statistically different from that for all blacks in the State (12.1 per 1,000), although the numbers were very small.

No significant association between proximity to industrial site and incidence of miscarriage was found. Further, no time trend in miscarriages was observed.

Summary

The overall documented miscarriage rate is 12.7% ± 1.6%, and the rate using both documented and undocumented miscarriages is 15.7% ± 1.7%. Miscarriages among white women are relatively well ascertained, and the rate is not statistically significantly higher than expected, given the age structure of the pregnant white women. The observed age-specific rates for single pregnancies do not exceed the rates found in several comparable historical studies. Black miscarriage rates are lower than white rates, but miscarriag s are less well ascertained, and a firm conclusion cannot be drawn on the basis of available data. However, the observed miscarriage rates for blacks are consistent with rates found in studies with similar ascertainment. The age-adjusted miscarriage rates are below the levels set out in the protocol as being elevated. Stillbirth ratios are based on very small numbers and are not statistically different from those of the entire State. The expert Technical Advisory Group reviewed the miscarriage rates and, on the basis of the criteria established in the protocol, judged that they were not elevated.

Recommendations

On the basis of analysis of the data collected and the criteria established in the protocol, the findings indicate that at this time further study of miscarriages in the area is not warranted.

To communicate these findings, we recommend 1) that study results be communicated to residents of East Iberville Parish in a general meeting and that subsequent smaller meetings be planned so that concerned citizens may have the opportunity to question the investigators about the conclusions, the strengths and the weaknesses of the study in an more intimate setting and 2) that women who intend to delay childbearing beyond age 30 consult with their physicians and health care providers concerning the risk of fetal loss with increasing maternal age.

With respect to future investigations of fetal loss we have two recommendations: 1) a model or standard protocol for miscarriage investigation should be developed so that results of studies in different populations can be compared; the protocol should include a standard questionnaire, multiple methods of ascertainment including the follow-up of individuals, evaluation criteria for assessing the level of ascertainment achieved, and the appropriate use of secondary data sources; and 2) standard decision guidelines should be developed for assessing the results of these studies.

This study was carried out by the State of Louisiana, Department of Health and Hospitals, Office of Public Health, through an independent contract with the Tulane University School of Public Health and Tropical Medicine and with the assistance of the Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services. The study was supported by funds from the Comprehensive Environmental Response, Compensation, and Liability Act Trust Fund by interagency agreement with the Agency for Toxic Substances and Disease Registry, Public Health Services, U.S. Department of Health and Human Services.

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2.10 Training

Because of the personal nature of the data collected, all the interviewers were women. Training for interviewers included 1) an explanation of the questionnaire, 2) instruction in the type of information to be gathered, 3) observation of a mock interview, 4) two practice interviews (one as an interviewer and one as a respondent), and 5) brief instruction in communication skills.

Training for abstractors included instruction on 1) the essential elements of the data collection form, 2) medical record procedures in hospitals, 3) medical terminology and 4) the format of the hospital chart.

2.11 Data Reliability

Interview data on live births were matched with vital records. This procedure allowed a check on case ascertainment and verification of information obtained in interviews.

Hospital and medical records from January 1, 1982, to December 31, 1987 were screened for data on pregnancy losses. This procedure identified women who had moved away from the study area or who had not volunteered for the study but who should be counted for complete ascertainment. These records also documented information participants gave during their interviews. A random sample of hospital records was reabstracted to ensure that data collection was reliable.

Each interview was reviewed by the project epidemiologist for completeness and consistency. If data were missing or ambiguous, the respondents were contacted again to supplement or clarify their answers. Confirmation of residence by mother's recall was considered acceptable.

Procedures were taken to avoid data collected from more than one source being included twice in the study. A unique code was assigned to each participant to ensure confidentiality.

2.12 Confidentiality of Records

Study staff, interviewers and abstractors were 1) instructed about the need for keeping information confidential, 2) told the consequences of failing to do so and 3) given examples of breaches of confidence. Records were designed so that the patient identification information and a study number was on the front page of the questionnaire. After the patient had been identified the study number was placed on each page of the questionnaire, and the front page was separated from the remainder of the form. The identifying information was placed in a locked file cabinet, accessible only to the principal investigators.

Computer access was limited to those involved with the study. Maste code lists were kept in a secured, password-protected, encrypted computer separate from all other study records. All questionnaires were stored in locked file cabinets.

2.13 Data Management

Data from the master phone list, questionnaire, health care provide records, hospital records of fetal losses, and vital records were entered a computerized data base using dBase III+. Data were edited for accuracy, consistency between variables and for completeness.

2.14 Statistical Methods

2.14.1 Measures of Incidence

Three estimates of overall miscarriage rates were used for summariz and comparison between this study and other studies. The incidence of f t loss can be estimated as follows (MIS = miscarriage, LB = live birth):

a) Miscarriage rates for all miscarriages in the study period (ALL)

$$\frac{MIS}{MIS + LB} \times 100$$

This rate is computed from the total number of miscarriages and births, including all those that resulted from any woman who had mul pregnancies.

b) Miscarriage rates for the first pregnancy (MIS^*) for each woman during the study period (FIRST):

$$\frac{MIS^*}{MIS^* + LB^*} \times 100$$

This rate is computed from the total number of miscarriages and births that resulted during the first pregnancy for each woman in th study period. This rate tends to be lower than the ALL pregnancies but higher than the following rate.

c) Miscarriage rates for a single random pregnancy (MIS^R) for each woman during the study period (RANDOM):

$$\frac{MIS^R}{MIS^R + LB^R} \times 100$$

A single random pregnancy is selected for each woman. If a woman only had one study pregnancy, that event is used. If a women had multiple pregnancies during the study period, then one pregnancy was chosen at random. This rate is computed from the number of those pregnancies that resulted in either miscarriage or live birth. It is lower than the rate based on FIRST or ALL pregnancies.

These formulas may be adjusted to account for age, race and status of documentation.

2.14.2 Statistical Analyses

a) Miscarriage rates from historical studies were compared with this study's rates by using standardized mortality ratios (SMRs) The choice of comparative study populations depended on the comparability of the study design.

b) Trends in time of miscarriage rates were examined by using logistic regression to find any evidence of increased incidence or of a tendency to cluster.

c) Using logistic regression, a crude and adjusted analysis of the geographic distribution of miscarriage rates was performed to assess the possibility of environmental factors associated with the location of plants in the area.

2.14.3 Rationale for Decision Guidelines

During protocol development the decision was made and approved not to select a comparison community to obtain expected rates of miscarriage. It is well documented that members of communities who believe that they have an exposure or health problem are more likely to volunteer, giving volunteer bias. The memory of miscarriage is also subject to recall bias, with individuals concerned about exposures expending more effort to recall events. In addition, other factors such as inbreeding which might occur in small communities could affect the rate of miscarriage in the comparison group but would be very difficult to assess. Thus, the investigators and the review groups agreed a more accurate comparison would be to use a range of rates of miscarriage, compatible with those found in large, well-designed and documented historical studies.

With the Technical Advisory Group, decision guidelines w re establish on the basis of a range of miscarriage rates computed from all documented pregnancies: miscarriage rates below 15% were to be considered normal; betw 15% and 24%, cause for examining known risk factors; and 25% and higher, re for further investigation. These ranges were selected on the basis of rece studies with high ascertainment of pregnancies. Miscarriage rates for the under-35 group range from 11% to 16% and for the 35-and-higher age group, f 25% to 28% (Mills et al., 1988 and Wilcox et al., 1981). Depending on the distribution of the pregnant women, miscarriage rates could be expected to from 15% to 20%, assuming ascertainment of approximately that found in thes studies. This range allows for variation in the age distribution of the population: it assumes that study results 1) show relatively complete ascertainment of pregnancies and 2) document completely the outcome of thes pregnancies.

Hertz-Piccioto and Samuels (1988) show that in prospective studi s th average miscarriage rate has varied between 11.7% and 14.6%. These rates a not adjusted for age or any other factors. In studies of older wom n with ascertainment of pregnancy and excellent documentation, miscarriage rates greater than 20% may be found. In studies of younger women with poor ascertainment of pregnancy and poor documentation, however, the miscarriage rates found may be much lower.

Although comparison of crude miscarriage rates with a normal range is appealing in its simplicity, variation of rates due to age differences in comparison groups is an important factor and must be controlled for. Therefore, age-adjusted comparisons with other studies were also performed. The level of ascertainment, documentation and study design were also consid in these comparisons.

2.14.4 Sample Size Considerations

In this study, we do not have a large number of pregnancies with whic establish precise estimates of miscarriage rates; therefore, sampling variability is to be expected. Sample estimates of miscarriage rates may exceed 15% by chance alone and still be consistent with the normal range. samples of size 188 (the number of pregnancies ending in a docum nted miscarriage or live birth in the white population), 80% and 95% confidence intervals have been computed for sample miscarriage rates of 15% and 20%. These confidence intervals are approximate, because the study rates include multiple births to many women. These multiple events are not independent.

80 % confidence interval:

$$.15 \pm 1.28 \sqrt{(.15)(.85)/188} = .15 \pm .03 = (.12, .18)$$

$$.20 \pm 1.28 \sqrt{(.20)(.80)/188} = .20 \pm .04 = (.16, .24)$$

95% confidence interval:

$$.15 \pm 1.96 \sqrt{(.15)(.85)/188} = .15 \pm .05 = (.10, .20)$$

$$.20 \pm 1.96 \sqrt{(.20)(.80)/188} = .20 \pm .06 = (.14, .26)$$

Assuming a true miscarriage rate of 15%, the chance of obtaining a sampl miscarriage rate exceeding 18% by sampling variability alone is less than 10%. Further, the chance of exceeding 20% is less than 2.5% by chance alone. Therefore, allowing for sampling variability and to be consistent with the normal range of miscarriage rates, the sample miscarriage rate should not exceed 20%.

3 RESULTS

3.1 Ascertainment of Eligible Study Population

Multiple methods of case ascertainment were employed to identify the eligible study population. Recruitment methods included public notification, telephone screening and mail notification. Other methods of case ascertainmen employed included search of hospital and emergency room records to identify women who had had miscarriages and review of vital records to identify those with live births.

3.1.1 Recruitment Efforts

Recruitment efforts resulted in the interview of 200 eligible participants: 61 (31%) from public notification, 119 (60%) from telephone screening, 14 (7%) from mail notification, and 6 (3%) from other sources (community outreach, health clinic rolls) (Table 1).

Of 117 calls to the hot line (public notification), 36 simply wanted mor information. The remaining 81 volunteers were screened and 61 were found to b eligible under study criteria (Table 1).

Telephone screening attempted to contact every residential telephone number (1,085). Of these, 129 women had responded (hot line or mail) and no further contact was made. Of the remaining 956 numbers, 63 (7%) had been disconnected and 16 (2%) were never reached. Of the 877 phone numbers reached for screening, 19 (2%) refused to participate in the study, 739 (86%) indicate that no women in the household were eligible for the study, and 119 (14%) were found to be eligible and were interviewed (Table 1). The number of eligible women found in the telephone survey is less than expected. The crude birth rate for the area is about 22 per 1,000, so 739 households at 3 persons per household would be expected to produce about 243 live births to 232 women (1.05 live births per woman). Only 119 were ascertained as eligible, 51% of the number expected.

An initial mailing to all 1,163 residential mail boxes informed residents of the study and encouraged participation. Three subsequent mailings targeted addresses which had not responded to the public notification or to the previous mailing. Each mailing included a stamped return postcard for the conveni nce of the participant. This resulted in a total of 290 returned postcards. Of these, 182 (63%) had been identified by other recruitment efforts. The remaining 108 were screened for eligibility, and 17 were found to be eligible (none had previously been included in the study). Of these 17 women, 14 were interviewed; 3 refused to participate in the study (Table 1).

Comparison of live births among interviewed participants and live birt from vital records indicated that many women had not responded to the recruitment methods despite extensive efforts to encourage participation. Direct follow-up of the women identified through vital records was not permitted in this study protocol. Thus, the time for case ascertainment wa extended in an attempt to use community outreach to increase the participation. The parish health clinic encouraged potentially eligible wor seeking health care to participate in the study, as did church pastors and community leaders. Of 10 individuals identified, 4 were determined ineligi and 6 were interviewed and participated in the study (Table 1).

In summary, the recruitment effort contacted some 1,057 women in households in the area who were screened for eligibility; 22 refus d, 854 w classified as ineligible, and 200 were interviewed and determined eligible the study (Table 1).

3.1.2 Vital Records

Of 145 women identified through the Louisiana State Department of Vit Records as not having responded to previous recruitment efforts, 95 (67%) w never contacted by any means and their status is unknown; 36 (25%) were kno to have moved from the area; 10 (7%) were women who had refused to partici during earlier recruitment efforts; 2 (1%) claimed that they w re not eligi but vital records showed them to be eligible; and 2 (1%) were women we were unable to reach a second time in order to complete interviews that had been interrupted (Table 2).

3.1.3 Hospital Record Search

Hospital records search identified 12 women with miscarriages, 3 of wh agreed to complete the study interview when contacted by the hospital. Data the remaining 9 miscarriages with partial fertility histories, complete to t extent possible without violating confidentiality, were supplied by the hospital (Table 2).

3.2 Ascertainment of Pregnancies

Vital records indicated that 388 live births were reported during the study period in East Iberville Parish. Eighteen of the births were determi not eligible because of residence or age criteria. During interviews, 200 participants reported 205 live births, 203 of which were matched with live births reported on the vital registration system: 191 births matched exactly and 12 matched closely within several days or with minor differences. Two women reported delivering live births in East Iberville Parish; however, thc births were not included in vital record data (Table 3).

A total of 203 confirmed live births were identified among 200 interviewed women during the study period in the designated area (Table 3). Twenty-five live births identified from th fertility histories of the interviewed women were excluded because they were delivered in another area.

Of nine stillbirths, two occurred outside the study area and were excluded. Of 65 miscarriages identified on interview, 5 took place out of the area and were excluded. Pregnancies ascertained on interviews which ended in induced abortion (4), ectopic pregnancy (2) or hydatidiform mole (1) were excluded. Fifteen women were pregnant at the time of the interview.

Vital records provided the means to identify eligible women who had not responded to the recruitment methods employed in this study. The 169 live births identified from vital records without corresponding interviews were sorted according to mother's date of birth to identify 145 women (Table 3). From the birth certificates the date of last live birth, date of last f tal loss, cumulative number of live births, and cumulative number of losses of fetuses of a gestational age below 20 weeks and 20 weeks and beyond were obtained. Those data were used to construct fertility histories for these women for the study period. These records provided a means to identify live births, miscarriages and stillbirths that might have occurred during th study period. In 5 of the 145 women reviewed, the order of the fertility history (i.e. whether birth preceded miscarriage or vice versa) was unclear. Howev r, both could not have occurred during the study period. In these five cases, an outcome between two competing pregnancies was chosen at random. Because these 145 women were not interviewed, live births, miscarriages and stillbirths occurring after the last live birth have not been ascertained. Twenty-one live births were identified, 5 with the date of delivery unknown and 15 within the study period; however, no records of the births were found in the birth certificates for the study area, so they are assumed to have taken place outside the study area and are thus excluded. The remaining live birth did not meet the age criteria. One stillbirth was identified on the birth certificat s and excluded because no verification could be found in a search of hospital and other vital records. Thirteen miscarriages were identified -- the date of delivery was unknown in 3, and the remaining 10 occurred during the study period. Search of records in local hospitals to confirm the occurrence of these 13 miscarriages was unsuccessful, so they were excluded.

Families that had moved from the area but left forwarding addresses were contacted to participate in the study. Thirty-six eligible women were known to have moved but could not be located. Their fertility histories, constructed from vital records, are included among those of the 145 eligible women who did not volunteer for the study. Ninety-five women were never contacted, and their residential status is unknown. Some of them may have moved without a forwarding address, and others may have remained in the community but chosen not to respond.

At least 36 multiple-family residences (two or more families residing under one roof and sharing one telephone and one mailing address for the entire household) were identified. According to a secondary source of information, each of the multiple-family households had at least one woman eligible for the study. In 14 of these residences, even though contact was established with one of the families, the study team was not referred to other families in the household, even when asked if there were other women in the household. In 13 of the residences, no families participated, and in only 9 of the residences did all of the families enter the study.

The search of hospital records and emergency room logs ascertained 12 additional miscarriages of women who did not volunteer for the study. Three these women agreed to be interviewed when contacted by the hospital.

In summary, 372 live births were identified to a total of 354 women, 20 births to 200 interviewed women (volunteers), 169 births to 145 wom n identified in vital records only (non-volunteers), and none to the 9 women (non-volunteers) identified in the hospital record search for miscarriages. Further, 7 stillbirths and 69 miscarriages were identified among these women.

3.3 Comparison of Volunteers and Non-Volunteers

For clinic or physician (but not hospital) medical records to be revie for documentation of a miscarriage, a signed medical release form was required. Thus, the characteristics of volunteers and non-volunteers is important, even though the data from volunteer and non-volunteer sources were pooled. When compared with study volunteers, non-volunteers were mor likely to be black (68% vs. 49%), under 30 years of age (75% vs. 50%), less educated (28% less than 12 years of education vs. 11%), and of lower gravidity (60% le than or equal to gravida 2 vs. 54%). They report similar numbers of stillbirths (98% with none vs. 96%) but fewer miscarriages (88% with none vs. 67%) (Table 4). These data are based on interview information for the volunteers and data available from the vital records at last live birth for t non-volunteers.

When the live births of non-volunteers are compared with those of volunteers, non-volunteers were more likely to be black (71% vs. 49%), under years of age (86% vs. 74%), less educated (28% with less than 12 years of school vs. 15%), and of lower parity (68% less than or equal to 1 vs. 75%). addition, non-volunteers reported slightly more deaths among their children with 1 or more vs. 2% with 1 or more), similar fetal deaths at less than 20 weeks gestation (88% with none vs. 86%), and similar fetal deaths at 20 we k of gestation and over (2% with 1 or more vs. 2%). Non-volunteers' births we more likely to be born in an earlier year (53% before 1985 vs. 30%) and to h fewer prenatal visits (55% with nine or fewer vs. 27%); however, the distribution of Apgar scores at 1 minute and 5 minutes were similar (Table 5 These data were based on the vital record data reported to the vital registration system for volunteers and non-volunteers.

In summary, racial, age and fertility differences are evident between volunteers and non-volunteers. In particular, a larger percentage of the wh women volunteered compared to black women (102 of 150 (68%) compared with 97 202 (48%)). Further, volunteers tend to be older and to have experienced mo miscarriages than non-volunteers.

3.4 Documentation of Outcome

3.4.1 Documentation of Live Births

Documentation of each pregnancy reported was attempted. Of the 205 li births reported in the intervi ws, 203 (99 p rcent) were documented in vital records. Two live births reported to have occurred in the study period coul

not be documented and were excluded. The 169 live births to women identified through vital records alone (non-volunteers) are considered document d. The total documented live births are thus 372 (Table 6).

On interview, 25 live births to study women were identified that did not meet study criteria, and they were excluded. Through review of vital records, an additional 20 live births to non-volunteers (none of which were included in the study) were identified. Of these 20 births, 5 had an unknown delivery date, and the remaining 15 were in the study period; however, in a complete review of vital records throughout the study period, none of these live births were confirmed by review of birth certificates for the study area and are thus excluded (Table 6).

3.4.2 Documentation of Stillbirths

Of nine stillbirths identified from interviews, six were documented in medical records, and one could not be documented in reported stillbirth records (Table 6). Three stillbirths were excluded as nonstudy pregnancies -- two identified in interviews and one identified through vital records.

3.4.3 Documentation of Miscarriages

Of 69 miscarriages identified from interviews and hospital record searches, 54 (78%) were documented in medical records. Of the 15 remaining reported miscarriages, 9 were undocumented miscarriages, and 6 were undocumented pregnancies. Miscarriages were undocumented for the following reasons: health care provider did not have a record of the miscarriage (1); participants did not provide medical release (5); only proof of pregnancy was a home pregnancy test without medical confirmation (3). Reasons for six unconfirmed pregnancies included medical record information showed no indication of pregnancy but another condition (4) and woman said she thought she was pregnant, but had never undergone any pregnancy test including a home test (2) (Table 6).

Review of pregnancy history on vital records for non-volunteers showed an additional 13 abortions, either spontaneous or induced: 3 with the date of delivery unknown and 10 occurring in the study period. The residence of the mothers at the time of abortion was unknown, and the hospital search of miscarriages identified none of these women; thus, they are excluded. Further, five miscarriages identified during interviews were excluded because th y did not meet the study criteria for time or residence or both (Table 6).

Of 36 miscarriages reported by white women, 32 (89%) were document d compared with 22 of 33 (67%) miscarriages reported by black women. Failure to return the medical release forms was a major reason for nondocumentation among black women.

3.5 Consistency of Ascertainment and Interview Data

Of the 205 live births identified from interviews, 203 (99%) were documented. Only two women who claimed they were not eligible later were fo to have had live births in the study area.

Among interviewed women fertility histories were compared for consiste with information on vital records. When comparing interview and vital recor data, there was complete agreement for race, but minor discrepancies in year delivery (6 of 201 (2%)) and in total stillbirths reported (2 of 201 (1%)). Vital records report both spontaneous and induced abortions as fetal deaths under 20 weeks gestation. Vital records for 172 of 201 (86%) women had no record of spontaneous or induced abortion. In interviews, however, only 162 these same 201 (81%) women said they had never had a fetal death under 20 we -- statements that indicate some underreporting of fetal deaths on birth certificates.

3.6 Overall Miscarriage Rates in Comparison with the Normal Range

The overall documented miscarriage rate, based on documented miscarria and live births, is 12.7% ± 1.6% (rate ± SE) (Table 7). Although docum ntat of miscarriage is necessary for study integrity, miscarriages were reported which documentation could not be obtained. The rate based on all reported miscarriages, documented and undocumented, is 15.7% ± 1.7% (Table 7). The r of 15.7% may include events that were not really miscarriages, resulting in overestimation of the true rate. On the other hand, the rate of 12.7%, whic includes only documented miscarriages, may exclude some cases, resulting in underestimation of the true rate. The effect of possible miscarriages to non-volunteers who did not seek hospital care cannot be estimated.

Further examination of overall miscarriage rates shows a higher rate f whites than for blacks. This difference is due in part to the diff rences i completeness of documentation between the race groups. Among whites, 32 of miscarriages (89%) were documented, whereas among blacks, 22 of 32 miscarria (69%) were documented. The documented rate for whites was 17.4% ± 2.8% compared with 9.2% ± 1.9% for blacks (Table 7). Comparable rates for all miscarriages, including documented and undocumented cases, are 19.2 ± 2.9% a 13.2% ± 2.1% for whites and blacks, respectively (Table 7).

The likelihood of miscarriage increases with age, and white study wome at the time of pregnancy tended to be older than black women. Therefor , to compare black and white miscarriage rates, the rates are adjusted for age differences. The rates were standardized to the population of all black pregnancies. Age-adjusted documented rates are 15.1% ± 2.7% for whites and 9.3% ± 1.9% for blacks, and age-adjusted rates for all miscarriages, documen and undocumented, are 17.4% ± 2.9% for whites and 13.2% ± 2.1% for blacks. decrease in age-adjusted rates relative to unadjusted rates is due to the ol age of white women compared with black women. Miscarriage rates are greater for white women than for black women, even after age and level of documentat are adjusted. Because of consistent racial differences in ascertainment and documentation of miscarriages, the data were stratified by race and analyzed separately.

In summary, even after adjustment for age and documentation status, miscarriage rates were higher among whites than blacks. Some of the miscarriage rates when calculated by race, documentation status and age -- though not inconsistent with the range of normal miscarriage rates -- fall into the 15% - 25% range. As established in the protocol, these data were further evaluated.

3.7 Comparison of Miscarriage Rates with Other Populations

The comparison of overall miscarriage rates with a single normal range does not address the effect of important factors influencing the magnitude of miscarriage rates, including 1) completeness of ascertainment or completeness of coverage of the population, 2) how early the pregnancy was detected, 3) level of documentation, 4) age distribution of the reproducing population, and 5) length of time women were followed for pregnancy (for one pregnancy or for multiple pregnancies). This section examines these factors and compares study results with those found in several large-scale studies of spontaneous abortion.

3.7.1 Comparison of Overall Miscarriage Rates by Race, Type of Documentation and Definition of Rate

Overall and age-adjusted miscarriage rates were computed by race (white vs. black), status of documentation (undocumented included vs. document d only), and definition of miscarriage rate (ALL vs. FIRST vs. RANDOM).

The three definitions of miscarriage rates represent the various ways in which a woman's multiple pregnancies may be treated in analysis: 1) ALL, where all study pregnancies are included irrespective of whether they are multiple study pregnancies to an individual mother; 2) FIRST, when the first pregnancy in the study period is the only one included; 3) RANDOM, when the only pregnancy is selected or when a pregnancy is selected randomly from several qualifying pregnancies occurring in the study period. The computation of these three rates is required to compare data with other studies and to examine the effect of multiple study pregnancies among this group of women.

Miscarriage rates including all pregnancies (ALL) differed by race and documentation status even after adjusting for the differences in age between black and white women (Table 8): for whites, a 10% - 20% decline was noted with documentation; however, for blacks, a 25% - 40% decline was observed (Table 8).

When miscarriage rates were computed using the FIRST definition, rates decreased among whites, and black-white differentials in rates decreased for both the "undocumented included" and "documented only" groups (Table 8, age-adjusted rates). This finding suggests that multiple miscarriages are more likely to be a factor among whites than among blacks. Further investigation showed an excess of multiple miscarriages for white women in the over-35 age group. Seven of twenty pregnancies to women over 35 years of age resulted in

miscarriage; of these 7 miscarriages, 3 are single miscarriages; the other 4 are multiple miscarriages to 2 women. Little effect is evident among black women because they have relatively few repeat miscarriages. Of 15 pregnanci and 4 miscarriages among black women 35 year of age and over, 3 are single miscarriages, and 1 is a multiple miscarriage.

When miscarriage rates are computed by the RANDOM definition, miscarri rates decline still further for both black and white women and for both the "undocumented included" and "documented only" groups (Table 8, age-adjusted rates). This decline is explained by the fact that most miscarriages are followed by a live birth, provided sufficient time elapses for a second pregnancy.

In summary, the magnitude of a miscarriage rate depends on the definit of the rate -- ALL, FIRST or RANDOM -- and it can vary as much as 5%, depend on the extent of multiple miscarriages and length of follow-up. Miscarriage rates computed by the ALL definition will exceed those computed by the FIRST definition to the extent that multiple miscarriages occur in the population. Miscarriage rates computed by the FIRST definition exceed rates based on the RANDOM definition to the extent that sufficient time elapses for subsequent pregnancies.

3.7.2 Comparison of Cumulative Distribution of Miscarriages by Gestational A as a Measure of Early Ascertainment

Miscarriage rates decline with increasing gestational age, so the gestational age at which the pregnancy is detected will affect the magnitude the rates. Women with an earlier diagnosis of pregnancy (4-6 weeks gestatio thus will have higher miscarriage rates than those with a later diagnosis (6 weeks). Therefore, when comparing populations, one should consider the distribution of the gestational age at diagnosis of pregnancy. This measure may not be available, so a surrogate (the gestational age at the time of miscarriage) might be used. Figure 1 shows the cumulative distribution of gestational age at miscarriage for selected comparison populations and for t study.

The Insulin Dependent Diabetic (IDD) Study is a study of the incidence spontaneous abortion among normal women and insulin-dependent diabetic women (Mills et al., 1988). The IDD control group may provide the earliest ascertainment and most reliable diagnosis of pregnancy. This study enrolled women before (76%) or within 21 days (24%) after conception, as determined b menstrual history. Serum levels of beta-human chorionic gonadotropic (hCG) were measured 2 days after the expected first day of menstruation if menstruation had not begun. If the hCG value was equivocal, the test was repeated until a pregnancy was indicated or vaginal bleeding occurred. Once the pregnancy was established, control women were evaluated every 2 weeks during the first trimester. The median gestational age at the time of miscarriage was slightly less than 8 weeks, mean -- 8.7 $\pm$ 3.3 weeks, in the control group (Figure 1).

The Menstruation and Reproduction History (MRH) Study is a prospective study of freshman women at the University of Minnesota. Study participants report d the first and last days of each menstrual period on a calendar card with reasons for disrupted cycles. The status of pregnancy outcome was collected annually. Between 1935 and 1939, 1,984 women volunteered. Between 1961 and 1965, an additional cohort of 1,276 women was recruited and followed. No documentation of miscarriage was required in this prospective study. The median gestational age at miscarriage was 8.5 weeks; the mean age was about 9.6 weeks -- slightly later than for the IDD controls (Figure 1).

The Collaborative Perinatal Project (CPP) collected data on reproductive histories in the years 1959 to 1966. Random samples were taken of essentially all women registering in the obstetrics clinics of 13 hospitals enroll d in the study. The hospitals tended to be in poor urban areas. Reproductive histori s were taken at the first visit for prenatal care. Data on the occurrence of spontaneous abortion before week 20 is restricted to the last nonstudy pregnancy. No information was available on the gestational age at miscarriage for these pregnancies.

The Health Insurance Program (HIP) Study involved pregnant women recruited from March 1958 through February 1960, two-thirds of whom began prenatal care during the first trimester of pregnancy. Fetal deaths met the following criteria: microscopic findings indicating pregnancy, positive AZ test or definitive clinical diagnosis. Gestational age was defined as th interval between the first day of the woman's last menses and the expulsion of the fetus or the fetal, placental or decidual tissue. The median gestational age at miscarriage was 11 weeks; the mean age was 11.5 $\pm$ 3.4 weeks, substantially later than for IDD and MRH miscarriages (Figure 1).

In summary, the age distribution for IDD miscarriages is similar to that of MRH miscarriages -- median gestational age of 8 weeks vs. 8.5 weeks for IDD and MRH miscarriages, respectively, suggesting that gestational age at diagnosis of pregnancy is similar in the two studies. HIP miscarriag s, on the other hand, have a later median gestational age of 11 weeks when compared with the others, suggesting the omission of early miscarriages (Figure 1).

A review of documented and undocumented miscarriages among white women in this study shows a lower proportion (10% at 6 weeks) of early gestational age miscarriages, suggesting a later diagnosis of pregnancy for study women than for IDD (30% at 6 weeks) and MRH (20% at 6 weeks) participants. Requiring documentation for miscarriages shifts the distribution to slightly older ages (median gestational age is 8.5 to 9 weeks for "undocumented included" and "documented only" categories, respectively). The distribution of miscarriages among white women is closer to those in the MRH study than the HIP study (Figure 1).

Review of documented and undocumented miscarriages among black women shows a low proportion (15% at 6 weeks) of early gestational age miscarriages. Requiring documentation for miscarriages shifts the distribution to older ages (the median gestational age is 11.5 weeks to about 12 weeks for "undocumented included" and "documented only" categories, respectively). Distribution of miscarriages among black women is closer to those reported in the HIP study (Figure 1).

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TABLE 1

RECRUITMENT EFFORT: METHODS OF IDENTIFICATION OF VOLUNTEERS

METHOD	NUMBER
Public Notification:	
Total calls to hot line	117
Not eligible - requesting information only	36
Not eligible	20
Eligible and interviewed	61
Telephone Screening:	
Total residential telephone numbers	1,085
Households already responded	129
Disconnected numbers	63
Never able to contact	16
Refused to participate	19
Not eligible	739
Eligible and interviewed	119
Mail Notification:	
Total number of mail boxes	1,163
No response	873
Identified by other methods	182
Not eligible	91
Refused to participate	3
Eligible and interviewed	14
Other (Community Outreach):	
Screened for eligibility	10
Not eligible	4
Eligible and interviewed	6

TABLE 2

IDENTIFICATION OF NON-VOLUNTEER WOMEN FROM SECONDARY SOURCES
(VITAL STATISTICS AND HOSPITAL SEARCH*)

SOURCE	NUMBER OF WOMEN
Vital Records:	145
Never able to contact[1]	95
Moved from area	36
Refused to participate (Data from another source)	10
Claimed not eligible (Data from another source)[2]	2
Incomplete interview[3]	2
Hospital Search:	
Miscarriages identified through hospital search but women not interviewed	9
Women identified from secondary sources	154
Women identified from study recruitment methods[4]	200
TOTAL WOMEN IDENTIFIED	354

* Records of these women who could not be contacted by study recruitment methods were partially completed from vital statistics records.

1 No telephone or did not respond to telephone or mail recruitment.

2 Claimed not eligible during recruitment attempts but records found in vital statistics.

3 Interview was begun but not completed. Participant could not be contacted again; vital records were used to complete information.

4 Includes three women originally identified through hospital search. Hospital contacted women who agreed to be interviewed.

TABLE 3

COMPARISON OF LIVE BIRTHS REPORTED FROM INTERVIEW WITH VITAL RECORDS

SOURCE	NUMBER OF WOMEN
Live Births Reported from Vital Records:	
Live births reported for East Iberville Parish	388
Not eligible [age and residence criteria]	18
Eligible live births reported	370
Live Births Reported from Interviews:	205
Matched exactly with vital records	191
Matched approximately	12
Unable to document in vital records	2
Live births from interviews of 200 women documented in vital records (volunteers)	203
Live births from vital records of 145 women (non-volunteers)	169
Total live births identified and documented	372

(To 354 women, including 9 women who had miscarriages that were identified only through hospital search)

TABLE 4

COMPARISON OF CHARACTERISTICS OF WOMEN
VOLUNTEERS AND NON-VOLUNTEERS

VARIABLE	VOLUNTEERS (INTERVIEWED) n (percent)	NON-VOLUNTEERS (VITAL RECORDS ONLY) n (percent)
Total:	200	145
Race:		
White	102 (51)	46 (32)
Other than white	99 (49)	99 (68)
Age as of 12/31/87:		
15-19 years	4 (2)	7 (5)
20-24 years	43 (22)	52 (36)
25-29 years	52 (26)	49 (34)
30-34 years	63 (32)	25 (17)
35 years and older	38 (19)	12 (8)
Education:		
Less than 8 years	2 (1)	4 (3)
9-11 years	19 (10)	36 (25)
12 or more years	179 (89)	99 (68)
Unknown	- - -	6 (4)
Total Number of Pregnancies:		
1	42 (21)	47 (32)
2	65 (33)	40 (28)
3	54 (27)	29 (20)
4	39 (20)	29 (20)
Total Number of Stillbirths:		
0	191 (96)	142 (98)
1	8 (4)	3 (2)
2 - 4	1 (0.5)	0 (0)
Total Number of Miscarriages:[2]		
0	133 (67)	127 (88)
1	53 (27)	14 (10)
2	11 (6)	2 (1)
3 - 4	3 (1)	2 (1)

[1] Nine women identified through hospital search and never interviewed omitted.

[2] For non-volunteers (vital records only). Includes induced and spontaneous abortions.

TABLE 5

COMPARISON OF CHARACTERISTICS OF LIVE BIRTHS
VOLUNTEERS AND NON VOLUNTEERS

VARIABLE	LIVE BIRTHS TO VOLUNTEERS n (percent)	LIVE BIRTHS TO NON-VOLUNTEERS n (percent)
Total:	201[1]	169
Race:		
White	102 (51)	48 (28)
Other than white	99 (49)	121 (72)
Age at delivery:		
15-19 years	32 (16)	49 (29)
20-24 years	57 (28)	71 (42)
25-29 years	61 (30)	25 (15)
30-34 years	40 (20)	18 (11)
35-50 years	11 (6)	6 (4)
Parity (not including this birth):		
0	80 (40)	60 (36)
1	71 (35)	54 (32)
2	34 (17)	36 (21)
3	12 (6)	12 (7)
4 or more	4 (2)	7 (4)
Deaths Among Live Births:		
0	198 (99)	161 (95)
1	3 (2)	5 (3)
2	0 (0)	3 (2)
Fetal Deaths at Less Than 20 Weeks:		
0	172 (86)	148 (88)
1	23 (11)	16 (10)
2 or more	6 (3)	5 (3)
Fetal Deaths at More Than 20 Weeks:		
0	197 (98)	166 (98)
1 or more	4 (2)	3 (2)

[1] Of 203 documented live births reported on interview and verified by vital records, 2 were verified, but data on the birth certificates were not available.

TABLE 5 continued

COMPARISON OF CHARACTERISTICS OF LIVE BIRTHS
VOLUNTEERS AND NON-VOLUNTEERS

VARIABLE	LIVE BIRTHS TO VOLUNTEERS n (percent)	LIVE BIRTHS TO NON-VOLUNTEERS n (percent)
Total:	201	169
Education:		
Less than 8 years	3 (2)	4 (2)
9-11 years	27 (13)	44 (26)
12 years or more	171 (85)	118 (70)
Unknown	0 (0)	3 (2)
Year of Delivery:		
1983	32 (16)	48 (28)
1984	28 (14)	42 (25)
1985	47 (23)	30 (18)
1986	52 (26)	24 (14)
1987	42 (21)	25 (15)
Prenatal Visits:		
0	4 (2)	2 (1)
1-9	49 (25)	90 (54)
10-12	85 (43)	48 (29)
13 or more	62 (31)	28 (17)
Unknown	1 (.5)	1 (.5)
APGAR (1 minute):		
1-4	9 (4)	12 (7)
5-7	30 (15)	23 (14)
8-10	162 (81)	131 (79)
APGAR (5 minutes):		
1-9	19 (10)	20 (12)
9	169 (84)	133 (80)
10	13 (6)	13 (8)

TABLE 6

IDENTIFICATION AND DOCUMENTATION OF PREGNANCIES

REPRODUCTIVE OUTCOME	Documented	Not Documented	Excluded
Live births	372	0	47[1,2,3]
Stillbirths	6	1	3[4]
Miscarriages	54	15[5,6]	18[7,8]

1 Twenty-five live births identified at interviews did not meet study criteria (out of area) and were excluded.

2 Twenty live births were identified during review of birth certificates of non-volunteers: 5 with date of delivery unknown and 15 within study period but residence of mother unknown. No record of birth in East Iberville during study period was found, so these 20 births were excluded.

3 During the interview, two women claimed live births in the study area during study period. The births could not be documented in vital records and are excluded.

4 Three stillbirths (two found during interview and one in vital records) were excluded because they did not meet study criteria.

5 Includes nine miscarriages claimed during interviews but for which no documentation in medical records was available.

6 Includes six unconfirmed pregnancies claimed during interviews but for which no documentation was available.

7 Five miscarriages identified during interview did not meet residenc criteria and were excluded.

8 Thirteen spontaneous and induced abortions at less than 20 weeks' gestation were identified during review of birth certificates of non-volunteers: 3 with date of delivery unknown and 10 during the study period. Residence of the mother at time of event is unknown. No records of these were found in the hospital search; therefore they are excluded.

TABLE 7

OVERALL MISCARRIAGE RATES

	Miscarriages n	Live births n	Miscarriage rate percent[1]	SE[2] percent
Documented:				
Total[3]	54	372	12.7%	1.6%
White	32	152	17.4%	2.8%
Black	22	218	9.2%	1.9%
All Miscarriages (includes documented and undocumented):				
Total[3]	69	372	15.7%	1.7%
White	36	152	19.2%	2.9%
Black	33	218	13.2%	2.1%

1 Rate =Miscarriages/(Miscarriages + Live births) X 100.

2 SE = Standard Error = $\sqrt{pq/n}$ (estimate of the sampling error of the rate

3 Total includes two births to women of other races.

TABLE 8

MISCARRIAGE RATES BY RACE, DOCUMENTATION AND MULTIPLICITY STATUS

CRUDE AND AGE-ADJUSTED

NO AGE ADJUSTMENT

	Undocumented Included		Documented Only	
Miscarriage Rate:	White	Black	White	Black
*ALL	19.2 ± 2.9	13.2 ± 2.1	17.4 ± 2.8	9.2 ± 1.9
#FIRST	16.8 ± 3.1	14.3 ± 2.5	15.1 ± 3.0	10.6 ± 2.2
+RANDOM	14.1 ± 2.9	12.2 ± 2.3	11.7 ± 2.7	9.4 ± 2.1

AGE ADJUSTED **

	Undocumented Included		Documented Only	
Miscarriage Rate:	White	Black	White	Black
*ALL	17.4 ± 2.9	13.2 ± 2.1	15.1 ± 2.7	9.2 ± 1.9
#FIRST	16.1 ± 3.0	14.3 ± 2.5	13.9 ± 2.9	10.6 ± 2.2
+RANDOM	14.0 ± 3.2	12.2 ± 2.3	11.1 ± 2.8	9.4 ± 2.1

*ALL = multiple pregnancies included.
#FIRST = the first pregnancy in study period used.
+RANDOM = a single, random pregnancy for each woman during the study period.

**Direct standardization to age structure all pregnancies among blacks, including the undocumented.

TABLE 9

AGE-SPECIFIC, AGE-ADJUSTED MISCARRIAGE RATES (PER 100 PREGNANCIES) AND PERCENT WITH GESTATIONAL 8 WEEKS OR LESS FOR SELECTED POPULATIONS

	MOTHERS' AGE						GESTAT AGE
Population	<20	20-24	25-29	30-34	35+	Age-Ad[1]	≤8 w
IDD[3]	--	13.6	14.6	16.1	25.0	16.5	5
MRH[4]	--	11.2	12.3	13.9	27.7	15.1	4
CPP[5]-White[6]	10.0	11.2	12.9	13.8	18.7	13.7	--
CPP[5]-Black[7]	9.1	12.0	14.7	15.5	17.1	14.6	--
HIP[8]	--	7.7	8.5	12.3	17.7	10.9	1

RATES OF THIS STUDY'S DOCUMENTED MISCARRIAGES (NUMBER OF MISCARRIAGES AND LIVE BIRTHS)

White							
*ALL	6.7(15)	13.8(58)	15.1(53)	21.1(38)	35.0(20)	20.1	30
#FIRST	7.1(14)	14.6(48)	15.9(44)	17.2(29)	18.2(11)	16.4	30
+RANDOM	8.3(12)	11.1(45)	12.8(47)	13.8(29)	8.3(12)	11.9	30
Black							
*ALL	8.9(56)	5.2(71)	11.5(52)	7.5(40)	26.7(15)	11.8	12
#FIRST	10.6(47)	6.9(58)	12.2(41)	10.3(29)	23.1(13)	12.5	12
+RANDOM	9.3(43)	6.4(63)	9.5(42)	10.0(30)	23.1(13)	11.4	12

*ALL = multiple pregnancies included.
#FIRST = the first pregnancy in study period used.
+RANDOM = a single, random pregnancy for each woman during the study period

1 Age-adjusted to the HIP population: Under 20, none: 20-24, 1,385: 25-2 2,222: 30-34, 1812: 35 and over, 1,190.
2 Percent of miscarriages with gestational age less than or equal to 8 w
3 Insulin Dependent Diabetic (IDD) Study
Early diagnosis of pregnancy, documented, single pregnancy, white.
4 Menstrual and Reproductive History (MRH) Study
Early diagnosis of pregnancy, self-reported, multiple pregnancies, whit
5 Collaborative Perinatal Project (CPP)
6 Retrospective-last nonstudy pregnancy, self-reported, single pregnancy, white.
7 Retrospective-last nonstudy pregnancy, self-reported, single pregnancy, black.
8 Health Insurance Program (HIP) Study
Late diagnosis of pregnancy, documented, 86% white.

TABLE 10

STANDARD MORTALITY RATIOS (SMRs) COMPARING DOCUMENTED, AGE-ADJUSTED STUDY MISCARRIAGE RATES TO SELECTED POPULATIONS BY RACE AND TYPE OF RATES

COMPARISON POPULATION	STUDY POPULATION	*ALL	#FIRST	+RANDOM
IDD[1]	WHITE	1.2	1.0	0.8
	BLACK	0.6	0.7	0.6
MRH[2]	WHITE	1.3	1.2	0.9
	BLACK	0.7	0.8	0.9
CPP[3]	WHITE	1.3	1.2	0.9
	BLACK	0.7	0.8	0.7
HIP[4]	WHITE	1.8**	1.6***	1.2
	BLACK	1.0	1.1	1.0

** $p \leq .01$
*** $.01 \leq p \leq .05$

*ALL = multiple pregnancies included.
#FIRST = the first pregnancy in study period used.
+RANDOM = a single, random pregnancy for each woman during the study period.

1 Insulin Dependent Diabetic (IDD) Study
2 Menstrual and Reproductive History (MRH) Study
3 Collaborative Perinatal Project (CPP)
4 Health Insurance Program (HIP) Study

TABLE 11

MISCARRIAGE RATES FOR GEOGRAPHIC AREAS AT
SPECIFIED DISTANCE FROM AN INDUSTRIAL SITE

DISTANCE	MISCARRIAGE RATE
White	
Less than .5 mile	22% (10/ 45)
.5 - 1 mile	25% (7/ 28)
Over 1 mile	16% (16/102)
Black	
Less than .5 mile	13% (17/135)
.5 - 1 mile	8% (6/ 77)
Over 1 mile	20% (2/ 10)

TABLE 12

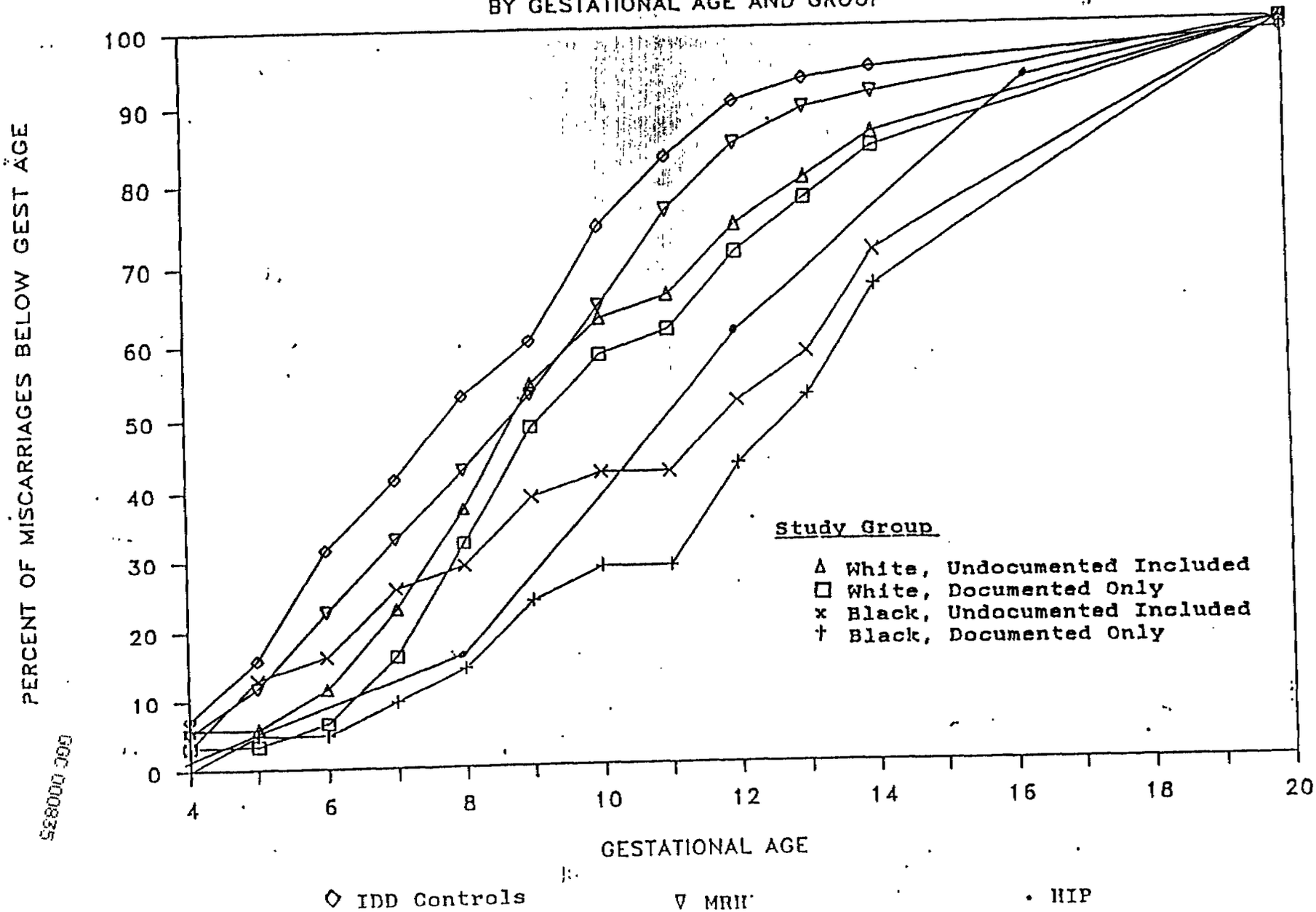
DOCUMENTED MISCARRIAGE RATES BY YEAR OF CONCEPTION

YEAR OF CONCEPTION	MISCARRIAGE RATE
1982-83	11.0%
1984-85	14.4%
1986-87	12.2%

FIGURE 1

CUMULATIVE DISTRIBUTION OF MISCARRIAGES

BY GESTATIONAL AGE AND GROUP



APPENDIX I

HOSPITALS IN THE EAST IBERVILLE PARRISH, LOUISIANA, STUDY AREA

ASCENSION GENERAL HOSPITAL
615 E Worthey Rd, P.O. Box 1029
Gonzales, LA 70707
PARISH: Ascension
PHONE: (504) 647-2891
ADMINISTRATOR: Keith Rush

NOTE: No formal Obstetrics/Gynecology
All patients sent to
E.K. Long or
Woman's Hospital

AMI RIVERVIEW MEDICAL CENTER
1125 Highway 30 West
Gonzales, LA 70737
PARISH: Ascension
PHONE: (504) 647-5000
ADMINISTRATOR: Ward Boston III

NOTE: No Obstetrics/Gynecology

LANE MEMORIAL HOSPITAL
6300 Main Street
Zachary, LA 70791
PARISH: East Baton Rouge
PHONE: (504) 654-4511
ADMINISTRATOR: Charlie Massey

NOTE: Treat Obstetrics/Gynecology
Depends on condition
whether or not
patients stay
overnight.

OUR LADY OF THE LAKE HOSPITAL
5000 Hennessy Blvd
Baton Rouge, LA 70809
PARISH: East Baton Rouge
PHONE: (504) 765-6565
ADMINISTRATOR: Robert Davidge

NOTE: No Obstetrics/Gynecology
All patients sent to
Woman's Hospital.

WOMAN'S HOSPITAL
9050 Airline Highway
P.O. Box 15379
Baton Rouge, LA 70895
PARISH: East Baton Rouge
PHONE: (504) 927-1300
ADMINISTRATOR: Thomas Hightower

NOTE: Patients in danger of
aborting are treated
in the Treatment Room.
D&Cs are done
in Day Surgery unless
condition warrants hospital stay.

EARL K. LONG MEMORIAL HOSPITAL
5825 Airline Highway
P.O. Box 52999
Baton Rouge, LA 70805
PARISH: East Baton Rouge
PHONE: (504) 358

NOTE: Obstetrics/Gynecology.

MEDICAL CENTER OF BATON ROUGE
17000 Medical Center Drive
Baton Rouge, LA 70816
PARISH: East Baton Rouge
PHONE: (504)292-2470
ADMINISTRATOR: Jerry Moeller

NOTE: No Obstetrics/Gynecology
May open a unit in
February 89.

BATON ROUGE GENERAL MED CENTER
3600 Florida Blvd
P.O. Box 2511
Baton Rouge, LA 70806
PARISH: East Baton Rouge
PHONE: (504)387-7000
ADMINISTRATOR: Edgar Silvey

NOTE: No Obstetrics/Gynecology.

RIVER WEST MEDICAL CENTER
1725 River West Drive
Plaquemine, LA 70764
PARISH: Iberville
PHONE: (504)687-9222
ADMINISTRATOR: Roger Snell

NOTE: Treat Obstetrics/Gynecol
Depends on physician
and whether or not patie
stays overnight.

APPENDIX II

Technical Advisory Group

To meet the peer review requirements of ATSDR, an advisory group, composed of scientists with expertise in reproductive epidemiology, biostatistics, risk assessment and obstetrics and gynecology was convened before this investigation began. Its mission was to review the protocol and, at the end of the investigation, to review the results and conclusions.

The members of the Technical Advisory Group with areas of expertise and affiliation are listed below:

Dr. James S. Storer, Chairman, Medical Director, Charity Hospital of New Orleans, LA.

Dr. Kenny Crump, Risk Assessment, Clements Associates, Ruston, LA.

Dr. Joseph Miller, Obstetrics and Gynecology, Louisiana State University Medical School, New Orleans, LA.

Dr. Steven Samuels, Biostatistics, University of California, Davis, CA.

Dr. Zena Stein, Reproductive Epidemiology, Columbia University, New York, NY.

Comments from the Technical Advisory Group members on the final report are included in this Appendix.

State of Louisiana
DEPARTMENT OF HEALTH AND HOSPITALS
OFFICE OF CHARITY HOSPITAL AT NEW ORLEANS
1532 TULANE AVENUE
NEW ORLEANS, LOUISIANA 70140
PHONE - 504/568-2311
LINC/621-2311

Buddy Roemer
Governor

David L. F
Secre

June 8, 1989

Dr. LuAnn White
School of Public Health
and Tropical Medicine
Office of the Dean
1430 Tulane Avenue
New Orleans, Louisiana 70112

Dear Dr. White:

I have reviewed the report/draft of the St. Gabriel Miscarriage Study. It is my opinion that it is an excellent report and that every mechanism available for completion and accuracy was used. I agree that the data does not indicate that there is an excess in stillbirths and miscarriages in the Study community.

I find the report acceptable.

Please indicate to me any further action that may be needed.

Sincerely,

James S. Storer, M.D.
Associate Medical Director
Associate Dean for Clinical Affairs
Tulane School of Medicine

CLEMENT

K.S. Crump Division
Clement Associates Incorporated
1201 Gaines Street, Ruston, LA 71270
318-255-4800

Environmental and Health Science

May 31, 1989

LuAnn E. White, Ph.D.
Tulane University Medical Center
School of Public Health and Tropical Medicine
1430 Tulane Avenue
New Orleans, LA 70112

Dear Dr. White:

I have reviewed the final report of the St. Gabriel Miscarriage Study and I found it to be thorough and reliable. The comments I had on the earlier version have been substantially taken into account.

I did not see it noted anywhere in this draft that the marginal elevation in the rate of stillbirths that was observed among blacks is not statistically significant and therefore may be ascribed to statistical variation. You may wish to include this in the final report.

In my opinion, the conclusions drawn in the report are appropriate.

Please contact me if I can be of further assistance.

Sincerely,

Kenny S. Crump, Ph.D.
Executive Vice President

KSC/lmw

SCHOOL OF
MEDICINE IN NEW ORLEANS
Louisiana State University
Medical Center
1542 Tulane Avenue
New Orleans, LA 70112-2822
Telephone: (504) 568-4850

LSUMC

Department of Obstetrics and Gynecology
Section of Maternal/Fetal Medicine

DATE: March 2, 1989

TO: LuAnn White, PhD
Frances Mather, PhD

FROM: J. M. Miller Jr., M.D.

RE: St. Gabriel Miscarriage Study

Overall, the report seems quite through. Minor observations include

1. Table 5, 5 minute Apgar scores are usually divided <7 and 7 -10, although the division along the lines presented for 1 minute score is ok.

2. Page 3, paragraph 5 $\pm$ instead of +.

3. There appears to be an absence or under reporting in 4-6 week miscarriages. The problem of underascertainment remains to be addressed.

4. Non-white miscarriage is skewed to those > 12 weeks. This may represent a different process.

GGC 000841

Review of:
"St. Gabriel Miscarriage Investigation, East Bank of Iberville Parish
Final Report"

Reviewer:
Steven J. Samuels
Assistant Adjunct Professor
of Internal Medicine and of Obstetrics & Gynecology

Division of Occupational & Environmental Medicine, LEHR
University of California
Davis CA 95616

June 2, 1989

1. As a member of the Technical Advisory Group for the St. Gabriel study I have a long-standing familiarity with both the protocol and the interim draft reports. I have a professional interest in the measurement of the risk of miscarriage. As the report makes clear, it is not easy to compare miscarriage risks measured in different studies.

2. I completely agree with the conclusion that miscarriage rates in St. Gabriel are not elevated in comparison to those found in comparable studies.

3. I judge the study protocol to have been well executed. The Tulane group has an admirable record for eliciting community participation in health studies. The recruitment efforts in this investigation probably set a new standard to which other studies will be held. The failure to interview mothers of 55% of known live births is not alarming; California household surveys of two census tracts had similar non-interview rates. The racial difference in volunteer response and in documentation <u>is</u> troubling. In retrospect, the protocol should have allowed tracing and interview with a sample of mothers of non-volunteer births to evaluate the reasons for not volunteering. I do not believe that a more complete ascertainment of pregnancies among black women would change the study conclusions.

4. Out of concern for privacy, the study did not ask for or count pregnancies which ended in elective abortions. The inclusion of such pregnancies in the calculations would have lowered the measured risks somewhat (E. Susser reference in bibliography), bringing them more into line with the rates of clinical pregnancy in prospective studied reviewed by Dr. Hertz-Piccioto and myself (Hertz-Piccioto and Samuels reference in bibliography).

5. The community's original perception of a cluster deserves some comment. do not think that most people are aware of how high "normal" rates of miscarriage are (greater than 1 of 8 pregnancies). In part, this is because most miscarriages are "private" events, unlike, say, childhood cancer. As a result, when someone starts to count miscarriages, the number appears startling. Yet most people will, on reflection, know someone who has had at least one miscarriage. Communication of these facts to the community will be a real challenge, especially as the reasons for most miscarriages are unknown.

6. On a technical note, the miscarriage risk in St. Gabriel parish is lower than I would have anticipated. When a community is selected for study because of an apparent high rate or cluster, than a priori it will usually have a rate higher than average. Even with this selection bias, St. Gabriel turned out not to have a high-appearing rate when compared t the comparison populations.

7. As a member of the Technical Advisory Committee, I am aware of the reasons that a comparison community was not chosen (vital records comparisons of reported prior abortions had been done): a) the cost; b) nearby communities had potentially similar environmental risks; c) geographically distant communities had differing racial, cultural, and genetic characteristics; and d) comparison communities would probably have had lower response rates than St. Gabriel, leading to questions of response bias. The Advisory Committee agreed that a comparison study was not warranted, and this decision could have been made explicit in th report.

Columbia University in the City of New York | New York, N.Y. 10032

GERTRUDE H. SERGIEVSKY CENTER

630 West 168th Street
Tel.: (212) 305-6866

June 15, 1989

Dr. James Storer
Tulane Medical School
1430 Tulane Avenue
New Orleans, LA. 70112

Dear Dr. Storer:

I have read carefully your final report on the St. Gabriel Miscarriage study. As a consultant, I would like to say it was carefully carried out and followed very carefully the guidelines that were developed at the initial stages.

Sincerely,

Zena A. Stein
Associate Dean of Research
Professor of Public Health (Epidemiology)
Columbia University
Director
Epidemiology of Brain Disorders Department
New York State Psychiatric Institute

ZAS:ms