Birth Defects in Infants of Diabetic Mothers: A Historical Review

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ABSTRACT

Background: Over the past 80+ years, outcomes in diabetic pregnancies have improved remarkably. In the preinsulin era, both fetal and maternal deaths were common. After insulin was discovered, the likelihood of a successful pregnancy increased, but fetal losses were still common. By the end of the 20th century, a number of medical advances allowed women with diabetes to reasonably expect to deliver a healthy infant, although the perinatal mortality rate was twice that reported for women without diabetes. The excess losses were attributable to birth defects.

Objective: The purpose of this article was to use the recognition of, and approach to, birth defects in infants of mothers with diabetes as an example of the gradual evolution of clinical care and research from the dawn of the insulin era to the age of molecular biology.

Methods: Archival material from the Joslin Diabetes Center (Boston, Massachusetts) was used to document the early history of the problem. Particular emphasis was given to the writings of Priscilla White, MD. Illustrative articles, especially those cited in textbooks, were chosen to highlight developments over the mid to late 20th century.

Results: Before the discovery of insulin, maternal death was the primary issue in diabetic pregnancies. With the availability of insulin, the maternal death rate decreased sharply and fetal deaths became the preeminent problem. Many of these losses were due to iatrogenic prematurity complicated by respiratory distress syndrome; early deliveries avoided stillbirth in late gestation. In the last quarter of the 20th century, methods of assessing fetal well-being and lung maturity allowed pregnancies to proceed nearer to term. Birth defects then emerged as the leading cause of perinatal mortality. The risk for birth defects was linked to diabetes control early in the first trimester, and the mechanism was related to free oxygen radicals from excess glucose. Preconception programs have been shown to reduce the risk.

Conclusions: Clinical advances often are not dramatic. This article illustrates how resolution of a problem may evolve incrementally over decades. Birth defects, once unnoticed in infants of diabetic mothers, became a leading concern. It is now possible to reduce the incidence of these defects to levels seen in nondiabetic pregnancies. Epigenetic mechanisms responsible for malformations have been elucidated. (*Insulin*. 2009;4:169–176) © 2009 Excerpta Medica Inc.

Key words: birth defects, congenital malformations, maternal diabetes, infants of diabetic mothers.

INTRODUCTION

The primary purpose of this article was to review the history of the recognition and treatment of congenital malformations in infants of diabetic mothers (IDMs) over 80+ years, a topic in which I had an active interest during the late 20th century. A secondary purpose was to present a paradigm for biomedical investigation, noting that improvements in clinical care may be slow and incremental—occurring over decades, not years. Dramatic breakthroughs such as the discovery of insulin are distinctly uncommon.

When I joined the staff of the Joslin Clinic (Boston, Massachusetts) in 1974, it was 50 years after Priscilla White had joined Elliott Joslin's practice. She was about to retire after a lifetime in diabetes care and was the virtual founder of the field of obstetrical diabetes. For that reason, I consider her the Doyenne of Diabetic Pregnancy. Because I knew her and her patients, she has a major presence in this review, as does the Joslin Clinic.

Some disclaimers are needed. Data are presented as they were published because it was not possible to recast or redefine them to be consistent with present usage. Early papers often did not use the terminology we use today. For example, definitions of *fetal loss*, *perinatal loss*, and *gestational age of viability* have evolved over time. I have used the terms *birth defect* and *malformation* interchangeably. The elements used to define a *major malformation* were not standardized years ago and may vary even today. The term now generally includes defects that cause death, handicap, or disfigurement; require surgical correction; or are structurally significant (eg, unilateral renal agenesis).

Because the purpose of this article was to present a perspective and not to be a comprehensive review, I have selected illustrative references or reviews and not attempted to be all-inclusive. If a citation makes a point, it is used by itself.

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PRISCILLA WHITE, MD

Dr. White was born in 1900 (**Figure**). Clearly a bright young woman, she entered Radcliffe College in 1917 and Tufts Medical College in 1919. She could not go to Harvard Medical School because women were not admitted until 1945. For the same reason (gender bias), she could not be an intern in Boston, so she went to Memorial Hospital in Worcester, Massachusetts. While in medical school, she had worked with Elliott Joslin, who was impressed with "this early rising, young medical student"[1]; he invited her to join his practice in 1924.

The timing of her earliest exposure to diabetes is significant. In 1922, while she was still a medical student, insulin was first used to treat diabetes. It is hard to imagine what having diabetes meant for patients in the preinsulin era. Most of the diagnosed cases were symptomatic type 1 diabetes mellitus (DM). Patients who survived were cachectic, with almost no body fat. Thus, they could not oxidize free fatty acids and die of ketoacidosis. Recognition of this point led to treatment with near-starvation diets to preclude lipogenesis. Women were generally amenorrheic. Insulin therapy, crude as it was, allowed survival and, more to the point, allowed successful pregnancies.

Legend has it that White's interest in diabetic pregnancy developed because when she started her career at the Joslin Clinic, she, as a woman, was given female adolescents and teenagers as patients who began to bear children as they grew older. However, this cannot really be the case because her first chapter on diabetes in pregnancy was published in a Joslin textbook in 1928.[2] This was much too soon after her joining the practice for her young charges to have grown up, gone through puberty (which often occurred several years later than it does now), and then become pregnant.

Figure. Priscilla White, MD (circa 1930). Reprinted with permission from the Joselin Diabetes Center.

EARLY SUCCESS IN DIABETIC PREGNANCY

In her 1928 chapter,[2] White reviewed her Joslin Clinic experience with 58 women and 89 pregnancies. Most of these women developed diabetes during pregnancy, not before. Some of the cases were from the preinsulin era. She noted that diabetes was no longer a contraindication to pregnancy, meaning that heretofore it had been, and implying that many or most of the pregnancies occurred after 1922. She also observed that insulin therapy had decreased the frequency of sterility by allowing, over time, the resumption of the menstrual cycle.

Of the 89 pregnancies, only 56 came to term and, of those, only 42 were live births; 14 were stillbirths (**Table I**). She viewed this as an improvement. Losses included 13 spontaneous abortions (miscarriages) and 6 therapeutic abortions. Two deaths were related to prematurity, and 8 causes of death were unknown. A remarkable number was 4 fetal losses described as "undelivered," a euphemism for maternal death.

Birth defects were not mentioned. They may have been either absent or unrecognized. It is in this chapter that White made an often-quoted observation that "controlled diabetes is essential to fetal welfare."

Of the 58 women who conceived the 89 pregnancies, 16 were dead by 1926, including 10 patients who developed diabetes after the discovery of insulin and died despite having insulin-treated diabetes of short duration.

In her summary of this series, which spanned the transition from the preinsulin era to the early insulin era, she indicated that fetal mortality was >50% (47 losses among

Table I. Outcomes of 89 pregnancies (1928).[2]

Result	No. (%)
Losses	47 (53)
Living	42 (47)
Stillbirth	14 (16)
Spontaneous abortion (miscarriage)	13 (15)
Therapeutic abortion	6 (7)
Undelivered*	4 (4)
Premature	2 (2)
Unknown	8 (9)

*Maternal death.
Adapted with permission from the Joselin Diabetes Center.

89 pregnancies). The maternal mortality rate was nearly 5%, and more women died soon after pregnancy of unrelated causes. Congenital malformations were a nonissue.

Nine years later, White published another chapter in the Joslin text titled, "Pregnancy Complicating Diabetes."[3] This was a subtle choice of word order—not diabetes complicating pregnancy. Her title suggested that diabetes was the primary concern; pregnancy was a complication. The introductory paragraph noted an extraordinarily low overall success rate of live births (barely 50%), which was similar to her earlier data.

Stillbirth and spontaneous abortion remained major causes of unsuccessful pregnancies. The latter was linked to poor control, the former only tenuously so. These relationships persist today; first-trimester hyperglycemia increases the risk of spontaneous abortion, and subsequent hyperglycemia is related to macrosomia, but the role of hyperglycemia in stillbirth is less clear.

In her 1937 chapter,[3] White addressed the issue of birth defects; it was also an emerging concern for other clinicians. She indicated that 7 major defects occurred in 208 pregnancies seen in the pre- and post-insulin era (**Table II**).

She made a statement that bears reexamination: "Congenital defects are beyond our therapeutic control and are, we believe, related to a disease which is genetic in origin." She, in essence, threw up her hands.

We now know much about the etiology of birth defects and first-trimester hyperglycemia, so they are not beyond our therapeutic control. Moreover, they may not be genetic in the usual Mendelian sense, but are epigenetic in that dysmetabolism has been shown to alter gene regulation of embryogenesis.

The tenor of the times in diabetic pregnancy was such that the focus was shifting from preventing maternal mortality to preventing fetal mortality (spontaneous abortion) and perinatal mortality (stillbirth). Congenital malformations, even fatal ones, were, in the scheme of things, not terribly important given an overall success rate of ~50% live births, with <5% of the deaths being from malformations.

Another 9 years later, White's chapter in the 1946 Joslin text[4] noted only a single maternal death, which was 6 weeks postpartum and caused by hepatitis unrelated to diabetes. This death was part of a 10-year series of 271 pregnancies collected from 1936 through 1946. Consistent with this number, she commented that the Joslin Clinic was following 20 to 40 pregnancies at any given time, a volume that should produce 25 to 30 deliveries a year. This steady flow of patients was the beginning of a remarkable series of >2200 pregnancies, largely in women with type 1 DM. This was easily to become the largest series in the world and provided a gold mine of clinical data.

Table II. Malformations in 208 infants (1937).[3]*

Congenital heart disease (n = 2)
Atresia of gastrointestinal tract
Microcephaly
Achondroplasia
Mongolian idiot
Monster

*Malformation rate: 7/208 (3.4%).

Although maternal mortality was now a subsidiary issue, the incidence of fetal mortality remained high. She cited data that indicated overall loss rates of ~30% in the third trimester and ~60% over the entire course of pregnancy.

A section of the chapter,[4] headed "Fetal Abnormalities," included several adverse outcomes: macrosomia, jaundice, atelectasis (respiratory distress syndrome [RDS]), and congenital defects. Although the issue of birth defects was now clearly addressed, it was lumped together in a section with other conditions that were not the result of early embryogenesis. She again stated, "genetic origin appears to be the most logical explanation" for birth defects. Implicit in this view was a sense of predestination, which made prevention impossible. What is notable is that the percentages reported—12% malformations (fatal and nonfatal) in IDMs and 1.8% in infants of nondiabetic mothers (NDMs)—were similar to those reported today. However, the 12% included cretinism, feeble mindedness, and Mongolian idiocy, which we now don't consider to be birth defects; hence, the 12% would really be closer to 10%. Late 20th-century figures for birth defects were ~10% for IDMs and ~2% for infants of NDMs. Similar numbers obtained a half century before indicated that, by 1946, the Joslin series had become large enough to reliably estimate the magnitude of the problem.

A noteworthy historic observation appeared in this chapter: no fetus was lost to maternal ketoacidosis, as had been the case in earlier years. Diabetic ketoacidosis (DKA) still occurred, but it was no longer a frequent complication of pregnancy.

White's data are often difficult to interpret or poorly explicated. For example, the 1946 chapter[4] included a table of 309 pregnancies seen from 1898 through 1936. The accompanying discussion in the text was about 271 more recent cases (1936–1946); however, no separate tabulation was provided for that series. Sometimes her data in one paper overlapped those from other papers. She also published in obscure journals. To wit, in 1943, she published in the *Virginia Medical Monthly* a series of 125 pregnancies followed from 1936 to 1942.[5] In this series, the malformation rate was 18%. However, she said that the congenital defects contributed to only 1 of 17 fetal deaths and 1 infant death, and that the malformations were "most certainly not the chief or contributing cause of the deaths in sixteen other fetal deaths occurring in the third trimester or neonatal period." (What she called *fetal death* we would presumably now call *perinatal mortality*.)

She posited 3 causes for congenital defects: heredity, hormonal imbalance, and vitamin deficiency. The last suggestion is intriguing given what we now know about free oxygen radicals, neural tube apoptosis, and the antioxidant properties of some vitamins.

THE MIDDLE YEARS OF THE TWENTIETH CENTURY

As time progressed, patients seen in the third quarter of the century (1950–1975) had become diabetic in the insulin era and were followed during a time when there were many advances in medicine. Antibiotics and intravenous fluids were especially helpful given the prevalence of bacterial infections in diabetes and their role in causing DKA, which could now be treated more effectively.

In 1953, White wrote a review of diabetic pregnancy and concluded that maternal mortality was now practically nonexistent and that fetal survival was essentially 90%.[6] In 1958, she wrote an editorial,[7] in which she termed *hyaline membrane disease* (RDS) the most important cause of morbidity and mortality in the neonatal period. She tentatively suggested that the 3% mortality rate due to congenital anomalies might be partially lowered by avoiding anoxia due to maternal acidosis and hypoglycemia, or perhaps by reducing the severity of maternal vascular disease through better treatment of diabetes. Hypoglycemia has indeed been linked to neural tube defects in rat embryo cultures, but not clinically in humans. What is noteworthy in this editorial is the recognition of congenital defects as a significant cause of fetal mortality. By this time, fetal loss rates had been reduced to ~10%, meaning that the 3% due to birth defects represented a third of the losses.

White's great European counterpart, Jørgen Pedersen, had similar data. In 1964, his group published a review of congenital malformations in IDMs and noted an overall rate of 6.4%, with a 2.1% fatality rate—close to the 3% rate reported by White.[8]

At this point in time, a quarter century since the discovery of insulin and roughly midway through White's career, 2 dramatic improvements in diabetic pregnancy had occurred—the virtual elimination of maternal death and a much higher fetal survival rate. Nonetheless, fetal wastage was significant, mostly due to iatrogenic prematurity and consequent RDS. Deliveries were initiated preterm to avoid intrauterine fetal demise, which often occurred in the last 4 to 6 weeks of pregnancy. Fetal malformations were now recognized as significant, but minor, contributors to fetal loss. A body of experimental data recognized disordered metabolism as a cause of embryonic malformations in animal models, but no human data were available.

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THE MODERN ERA OF MANAGEMENT

During the third quarter of the 20th century, the fetal loss rate slowly declined to well below 10%. These data were included in a 1977 paper[9] about maternal vascular disease and pregnancy, which reviewed White's entire Joslin experience with >2200 patients seen since the discovery of insulin. In 1975, the last year included in this series, fetal survival at the Joslin Clinic and Boston Hospital for Women was 94%. It was at this juncture, coincident with White's retirement, that the modern era of management of diabetic pregnancy began.

Two new tests facilitated even greater improvement in fetal survival. First, pulmonary maturity could be assessed by doing an amniocentesis and measuring the lecithin-to-sphingomyelin ratio. Second, early fetal distress could be detected by finding fetal bradycardia in response to uterine contractions induced by oxytocin (ie, the oxytocin challenge test), or by simply monitoring the fetal heart rate without inducing contractions (ie, the nonstress test). Added clinical refinements were inhibition of premature labor with tocolytic agents and intrauterine induction of fetal pulmonary maturity by giving glucocorticoids to the mother. It was now possible to carry most diabetic pregnancies close to term and abandon arbitrary early delivery to avoid stillbirth.

The result of applying these advances and their refinements was an even further reduction in the perinatal loss rate, which could now be expressed as the number of losses per thousand, as opposed to percent survival. In the latter decades of the 20th century, perinatal mortality in diabetic pregnancies was ~30 to 40 per 1000, which was roughly double the overall rate in the United States. Because half the perinatal losses in IDMs were due to birth defects, virtually the entire excess mortality in diabetic pregnancies was caused by congenital malformations. It was a problem that could no longer be ignored.

A landmark article by Mills et al[10] in 1979 reviewed historical data for fetal malformations in the presence of preexisting maternal diabetes and noted those that were clearly more common. Mills et al then overlaid data about frequently affected organ systems on the known timeline for human embryology. An important resource for Mills et al was a 1971 paper by Kucera,[11] which reviewed the types of malformations seen in IDM. He noted a 200-fold increase in the caudal regression syndrome, a 20-fold increase in genitourinary defects, and a 2- to 4-fold increase in gastrointestinal (GI), cardiac, and other central nervous system malformations. Mills et al reached the nettlesome conclusion that teratogenesis occurred 2 to 6 weeks after conception or 4 to 8 weeks after the last menstrual period. The clinical implication of this observation was that the die was cast soon after a woman missed a period and realized that she was pregnant.

The first data providing a quantified link between first-trimester control and malformations were from the Joslin Clinic. They were presented orally to the American Diabetes Association in 1979 and then published by Miller et al[12] in 1981. Glycosylated hemoglobin (A1C) levels obtained no later than the end of the first trimester were used to retrospectively evaluate control during the teratogenic window. The series included 116 women who were followed at the Joslin Clinic and delivered at the Boston Hospital for Women. The overall malformation rate for these infants was 12.9%. The women were divided into 2 groups: 58 women in the better-controlled group had A1C levels ≤8.5%, and 58 women in the poorer-controlled group had A1C levels >8.5%. Infants of the women in the better-controlled group had a malformation rate of 3.4%; infants of the women in the poorer-controlled group had a malformation rate of 22.4% and included all of those with fatal defects (**Table III**).[12]

This was also the first study to quantifiably link the risk of any poor outcome in diabetes with glycemic control. The Diabetes Control and Complications Trial and UK Prospective Diabetes Study were not published until a decade later.

An obvious question now needed to be answered: could malformations be prevented? An East German study[13] published in 1983 reported a dramatic elimination of excess malformations in a group of women who were enrolled in a prepregnancy program and then rigorously treated once pregnant; unfortunately, A1C levels were not determined. The Diabetes in Early Pregnancy (DIEP) study,[14] a large multicenter study, was undertaken in the United States to try to answer the question. Hundreds of diabetic women at a number of centers were enrolled prepregnancy (the early-entry group). A group of nondiabetic women was also enrolled (the control group). The diabetic women measured their basal body temperatures and within 21 days of conception had a β-hCG test done to confirm pregnancy. They were briefly admitted to the hospital, and their diabetes was treated for the rest of the pregnancy according to the prevailing protocol at that institution. A third (late-entry) group was constituted subsequently and enrolled after the first trimester; their first-trimester A1C levels were not determined. After delivery, a standardized protocol for determining birth defects was used for all 3 groups.

The control group (NDMs) had a malformation rate of 2.1%—similar to what had been reported for half a century. The early-entry group had a malformation rate of 4.9%, but no link with A1C levels was found. The A1C results were expressed in unusual units: nanograms of fructose per 10 g of hemoglobin. The authors concluded that there was a "lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis" and thereby generated much controversy. In retrospect, the brouhaha was much ado about nothing. The level of glycemic control in the early-entry group was similar to that reported for the better-controlled group in the study by Miller et al.[12] The women at the Joslin Clinic had a malformation rate of 3.4%, comparable to that in the DIEP study.[14] The DIEP late-entry group had a rate of 9.0%, or about what would be expected in an unselected group of IDMs. Because their mothers were enrolled after the first trimester, no A1C data were available. This was an unfortunate lapse, because it is possible, if not likely, that their control was not as good as that in the study group, since these mothers were given no special attention early in their pregnancies. If that assumption is made, the results of the DIEP study were similar to those of the study by Miller et al at the Joslin Clinic.[12]

Table III. First-trimester glycosylated hemoglobin (A1C) levels and malformations (1981).[12]

A1C (No. of Women)	No. (%) of Fetuses Normal	Anomalies	Fatal
≤8.5% (58)	56 (96.6)	2 (3.4)	0
>8.5% (58)	45 (77.6)	13 (22.4)	6
All cases (116)	101 (87.1)	15 (12.9)	6

Despite the conclusion reached in this paper, the evidence for poor control being related to malformation risk continued to accrue. In 1989, another article by Greene et al[15] at the Joslin Clinic and Boston Hospital for Women looked at first-trimester glycemic control in 303 pregnancies, of which 250 reached viability. An increasing risk of birth defects with poorer control was documented. Poor first-trimester control was clearly related to fatal malformations. In that paper, HbA1, or total glycohemoglobin (A1a+b+c), was used to measure control. To allow for comparison of results from the 3 papers (Miller et al,[12] the DIEP study,[14] and Greene et al[15]), HbA1 results were expressed as SDs above the mean. The women in the better-controlled group (≤9 SD above the mean) had HbA1 levels and malformation rates (4.0%) similar to those found in the DIEP early-entry group and in the women in the study by Miller et al.[12] Also noted was an increasing risk of spontaneous abortion with poorer control (>9 SD above the mean). The finding of an increasing abortion loss rate with increasing first-trimester A1C levels was also noted in the DIEP results.[14] In the article by Greene et al,[15] only half of the 44 most poorly controlled patients (A1C levels >12 SD above the mean) delivered a live infant because of combined losses from spontaneous abortions or fatal malformations. Severe malformations are a cause of early pregnancy losses and may well have been a reason for the unusually high abortion rate.[16]

> Poor first-trimester control was clearly related to fatal malformations.

At this juncture, a general agreement had been reached on several points. Poor control in the first trimester, although variably defined, was related to teratogenesis. However, an elevated A1C level was only an indicator of increased risk, not a useful predictor of outcome in an individual patient.

Good control, also variably defined, lowered the risk of malformation in IDMs to 3% to 5%, but not as low as in NDMs (≤2%).

Evaluation and comparison of risk related to A1C levels will again be problematic once an international standardization of varying methodologies is completed. In any event, helping diabetic women who might become pregnant achieve A1C levels as near normal as feasible will remain desirable. Evaluation of risk by expressing A1C levels as SD above the mean likely will continue to be a useful tool.[17]

Evaluation of risk by expressing A1C levels as SD above the mean likely will continue to be a useful tool.

A number of centers in the United States and Europe instituted programs in the 1980s for diabetic women to improve their preconception control, which made more data available after publication of the 1983 East German study.[13] All the programs were successful in reducing malformation rates. Because the individual study groups were small, their degrees of success were difficult to evaluate. A review of the malformation rates in IDMs from several preconception programs found that the aggregate rate in nearly 500 pregnancies was as good as or better than the expected background (NDM) rate.[18] It could now be said that congenital defects were not really "beyond our therapeutic control." However, despite the success of prepregnancy programs, recruitment remains a barrier. Most women with diabetes do not enroll in a preconception program. Somehow the message is insufficiently promulgated or not taken to heart. Women who seek preconception care tend to be married, have higher incomes and educational levels, and have an ongoing relationship with their health care providers.[19]

Implicit in the recommendation for preconceptual care is avoidance of hyperglycemia in pregestational diabetes (type 1 or 2 DM). Gestational diabetes arising in late pregnancy does not cause first-trimester hyperglycemia.

Malformations of many organ systems can be detected using ultrasound in the second trimester. If the level of risk and/or anxiety is high, and the discovery of a serious or ultimately fatal malformation would lead the mother to terminate the pregnancy, ultrasonography should be done before 20 weeks. If termination is not an option, late second-trimester ultrasonography can be used to forewarn the pediatricians who will care for the infant. Amniocentesis can be used to supplement the ultrasound results in detecting neural tube defects.

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The expected types of defects remain similar to those initially reported by Kucera.[11] Cardiac defects include ventricular septal defect, corrected transposition of the great vessels, and aortic coarctation. Urinary defects include renal agenesis (unilateral and bilateral) and ureteral duplication. Sacral agenesis, spina bifida, and anencephaly are common, as are facial defects such as cleft palate. Duodenal and anorectal atresias occur in the GI tract.[20]

THE AGE OF MOLECULAR BIOLOGY

Given the now known relationship between glucose excess and teratogenesis, an obvious avenue of investigation was to clarify the mechanism(s). Following are illustrative examples from 2 laboratories (1 in Uppsala, Sweden, and 1 in Boston, Massachusetts), showing how underlying mechanisms of birth defects in IDMs have been investigated using sophisticated molecular biologic and epigenetic approaches. Both laboratories looked at neural tube defects in rodents, a common animal model used to study birth defects in diabetes. Much more work has been done; other mechanisms and organ systems have been examined. The examples given here are only intended to provide a glimpse of the body of work.

Eriksson, together with his colleagues in Uppsala,[21] was an important early contributor to sophisticated study in the field. Recognizing glucose as a provider of free oxygen radicals, he suspected that the use of oxygen-scavenging enzymes in the medium of a rat embryo culture model would prevent neural tube defects. He was able to demonstrate that growth retardation and neural tube defects were both diminished by the exhibition of superoxide dismutase or by using *N*-acetylcysteine to enhance synthesis of reduced glutathione.[21]

Akazawa[22] proposed a similar mechanism in rats with streptozotocin-induced diabetes. He also found that hyperglycemia increased reactive oxygen species, which reduced levels of glutathione and myoinositol.

Eriksson[23] made another important observation serendipitously. The Sprague-Dawley rats he used in Uppsala were supplied to him by a breeder in Hannover, Germany. At one point in his investigations, malformations and resorptions (the biological equivalent of abortion) ceased to occur with the expected frequency. After careful examination of his laboratory procedure and protocols, he contacted the breeder and discovered that the strain of rats had been changed. He then launched an investigation in a new direction. Because he still had rats in Uppsala from the old strain, he was able to try various cross-breeding combinations. He found that the different results were attributable to 2 isozymes of catalase, CS-1a and CS-1b.[23] The CS-1a isozyme was associated with the Uppsala strain, which was susceptible to neural tube defects. The new Hannover strain had the CS-1b variant and was resistant to the teratogenic effects of glucose (and β-OH butyrate). Although genetic differences in teratogenic susceptibility had long been known, Eriksson was able to relate a difference in 2 particular isozymes to the response to 2 diabetes-related teratogens, glucose and β-OH butyrate.

Loeken's laboratory in Boston added new information in the area of oxidative stress and genetic regulation of neural tube defects. She had an interest in Pax3, an important gene in the regulation of a protein (p53) that causes neural tube apoptosis in mice.[24] A cascade is started by hyperglycemia and oxidative stress (**Table IV**). Free oxygen radicals suppress Pax3, which ordinarily suppresses p53. Thus, in the presence of maternal diabetes, p53 rises and promotes neural tube apoptosis. Lowering of maternal glucose reverses the cascade.

Table IV. Cascade of Pax3 gene expression and neural tube defects.

Hyperglycemia increases oxidative stress
Free oxygen radicals suppress Pax3
Pax3 downregulates p53 protein
p53 protein is consequently increased
p53 protein causes neural tube apoptosis
Diabetes causes neural tube defects

In a review of oxidant regulation of gene expression, Loeken's coworkers described being able to induce neural tube defects with another oxidative stressor, Antimycin A.[25] They were also able to inhibit the deleterious effect of downregulation of Pax3 and the harmful excess of p53 in pregnant diabetic mice without treating the mothers' diabetes. Instead of lowering the glucose level, they provided the mice with chow enriched with an antioxidant, vitamin E.[25] The offspring of the diabetic mothers that were fed enriched chow had neural tube defects at the same rate as those of the nondiabetic control mothers. This finding evokes White's 1943 supposition that vitamins might be important in the etiology of birth defects and parallels the clinical observation that another antioxidant, folate, helps prevent neural tube defects in humans. Folate supplements have been added to cereal grains in the United States and Canada since 1998. The subsequent incidence of neural tube defects in all pregnancies appeared to have been halved.[26] Because it is hard to collect large series of birth defects in IDMs, the effect of folate supplementation in diabetic pregnancies remains to be seen.

Cardiac abnormalities in fetal mice have also been linked to Pax3 deficiency. Pax3 is necessary for cardiac neural crest (CNC) cell migration to the outflow tract. If Pax3 is not expressed because of oxidative stress, CNC-cell apoptosis ensues and outflow tract defects occur.[27]

The next frontier in the long history of approaches to the problem may be gene modification therapy in human pregnancy. The study of birth defects in IDMs can be viewed as a paradigm for biomedical investigation (**Table V**).

CONCLUSIONS

This article summarizes the history of the approach to birth defects in IDMs, which spans more than three quarters of a century. Our scientific knowledge and clinical capabilities develop and increase over time. We have moved from nonappreciation of the problem of birth defects, to resigned acceptance, to clinical investigation and therapeutic intervention, and finally, to elucidation of molecular and genetic mechanisms related to their etiology. Perhaps in the future, we may become more adept at modifying gene expression. Even so, the problem will persist. As long as maternal diabetes exists, so will its ill effects. We may yet become more effective in preventing and treating complications of diabetes, but prevention of diabetes, per se, is a history yet to be written.

Table V. Fetal malformations in infants of diabetic mothers: A paradigm for biomedical investigation.

Clinically irrelevant	1920–1940
Beyond therapeutic control	1940–1960
Of secondary interest	1960–1980
Related to glycosylated hemoglobin	1980–1990
Amenable to intervention	1990–2000
Molecular mechanisms	1990–2010
Gene modification	2010–2020

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