

# Advantages of Screening for Glucose Tolerance in the Sequential Weeks of Gestation

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## Abstract

Prelife exposure relates to development during the time preceding the first appearance of life, a time course from “conception to confinement.” From single cell zygote to finally formed fetus at confinement, a remarkable change occurs due to maternal fuels and hormonal influence on the fetal development. The crucial period in the fetal development is the first trimester. Early exposure to aberrant maternal metabolism in the embryonic developmental stage would result in congenital malformation and fetal wastage. Maintaining maternal glucose at the recommended level of fasting 80 to 90 mg and 2 hours postprandial plasma glucose 110 to 120 mg/dL during preconceptional period and throughout pregnancy is the assurance for the healthy offspring with ideal birth weight of 2.5 to 3.5 kg and prevention of noncommunicable diseases in the future.

## Keywords

- gestational diabetes mellitus
- glucose tolerance
- screening

## Introduction

David Barker's “Fetal Origin of Adult Diseases Theory” conceptualized that the body's susceptibility to “lifestyle” diseases was programmed in the intrauterine period. Intrauterine programming is a process whereby stimuli or stresses occurring at critical or sensitive periods of fetal development permanently change structure, physiology, and metabolism, thereby predisposing individuals to disease in adult life.<sup>2</sup> If the stimulus happens to be hyperglycemia in pregnancy, the consequent abnormal maternal metabolic environment affects the developing fetal tissues, organs, and control systems in complex ways that eventually lead to permanent functional changes in adult life. The quantum of hyperglycemic exposure in terms of duration and degree is relevant, as is the timing of the onset of exposure in the

course of pregnancy. Early exposure during fetal organogenesis and placental development has relatively more severe and lasting consequences than later exposure.<sup>3</sup> Depending on the timing and quantum of exposure to the aberrant fuel mixture, different effects may occur on the embryo-fetus including abortion, congenital anomalies, macrosomia, and large for gestational age, intrauterine growth restriction (IUGR) and small for gestational age, intrauterine death and still births, etc.<sup>4</sup> (►Table 1).

## Short-Term Hyperglycemia Complications in the Mother

- Increased infections
- Pregnancy-induced hypertension

**Table 1** Short-term complications in the offspring due to hyperglycemia

First trimester	Second trimester	Third trimester	Postpartum and neonatal
First 6 weeks postovulation—increased anomalies—diabetic embryopathy 3rd week—caudal regression syndrome 4th week—Spina bifida and anencephaly 5th week—Transposition of great vessels, renal anomalies 6th week—Ventricular septal defects, anal atresia, increased fetal wastage	Diabetic fetopathy Behavioral abnormalities Skeletal abnormalities—femoral hypoplasia Unusual facial phenotype Macrosomia	Diabetic fetopathy— Preterm labor, PROM, macrosomia, IUGR, IUFD, sudden intrapartum death	Diabetic fetopathy—Sudden intrapartum death, shoulder dystocia, birth injuries Increased perinatal mortality, respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, neonatal convulsions

- Hydramnios
- Macrovascular complications
- Instrumental deliveries
- Operative deliveries
- Obstetric palsies
- Puerperal sepsis.

### Long-Term Complications in the Mother<sup>5</sup>

- Women with gestational diabetes mellitus (GDM) have a high vulnerability for future type 2 DM, and GDM is considered the most reliable marker for it
- Cardiometabolic disorders in women.

### Long-Term Complications in the Offspring<sup>6</sup>

- Increased risk of early onset type 2 DM and obesity. Differences exist in the offspring; the risk of diabetes and obesity is based on time and type of diabetes exposure in utero.
- A negative correlation has also been shown between the severity of maternal hyperglycemia and the offspring performance on various neurodevelopmental and behavioral tests.
- Compared with children unexposed to diabetes in utero, children exposed to diabetes have been reported to be at higher risk of attention-deficit hyperactivity disorders
- Autism spectrum disorders.
- Intellectual disabilities.
- An interesting effect has been reported with combined exposure to maternal prepregnancy obesity and diabetes.

These effects have a proven possibility for prevention or delaying onset through appropriate postpartum lifestyle interventions.

### Time Course of Fetal Development from Conception to Confinement<sup>7</sup>

At the time of ovulation, after copulation, sperm travels through the cervix and uterus and into the fallopian tubes. Conception usually takes place in the outer third of the fallopian tube. A single sperm penetrates the egg and a fusion of the genetic information occurs. This resulting in a single cell is called a zygote (**►Fig. 1**).

The zygote spends the next few days traveling down the fallopian tube and rapidly multiplying into number of cells



**Fig. 1** Sperm entering egg. (Adopted from Prenatal Development by Dr. C. George Boeree.)

through division. A mulberry-like mass, 0.0254 cm wide, develops after the cell division. This ball of cells in the fallopian tube is called morula.

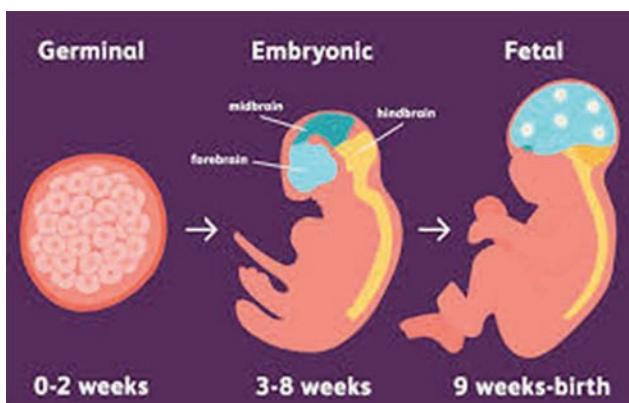
With additional cell division, the morula becomes a *blastocyst*, with an inner core and an outer shell of cells. The outer group of cells becomes the membranes that nourish and protect the inner group of cells, which becomes the fetus.

The blastocyst implants in the uterus between the 7th and 9th day after conception. At this point, the endometrium (the lining of the uterus) has grown and is ready to support a fetus. The blastocyst burrows into the endometrium where it receives nourishment. It is barely visible, but doubles every 24 hours. The placenta and supporting infrastructure for pregnancy develop at this time as well. It is estimated that up to 55% of zygotes never reach this phase of growth.

### The Embryo

The embryonic stage begins on the 15th day after conception and continues until about the 8th week, or until the embryo is 3 cm in length. During this period, the cells of the embryo are not only multiplying but also taking on specific functions. This process is called tissue differentiation. It is during this critical period of differentiation (most of the first trimester) that the growing fetus is most susceptible for damage from external sources (*teratogens*) including viral infections such as rubella radiation and (malnutrition) abnormal metabolites.

An embryo who has one developmental problem may have other problems that arose at the same time: Kidney problems and hearing defect, for example, are often found



**Fig. 2** Neural development. (Adopted from Development Psychology by Dr. Kendra Cherry.)



**Fig. 3** Eye and ear development. (Adopted from Healthy Lifestyle, Pregnancy Week by Week by Mayo Clinic Staff.)

together because both kidneys and the inner ears develop at the same time.

**Week 3**—The formation of the heart, the beginning of development of the brain and spinal cord, and the beginning of the gastrointestinal tract take place (►Fig. 2).

Between 18 and 19 days after fertilization, the heart begins to form. This early development is critical for subsequent embryonic and prenatal development. The heart is the first functional organ to develop and starts to beat and pump blood at day 21 or 22.

Teratogens introduced in this period may cause several problems such as the absence of one or more limbs or a heart that is outside of the chest cavity at birth.

**Weeks 4 and 5**—The embryo is 6 mm long: The formation of the vertebra, the lower jaw, the larynx, and the rudiments of the ear and eye begins. The heart, which is still outside body, now beats at a regular rhythm. The arm and leg “buds” are visible with hand and foot “pads” (►Fig. 3).

Teratogens may cause very serious problems involving the esophagus, vertebrae, and eyes. The infant could be born with severe facial clefts or missing hands or feet.

**Week 6** (12.7 mm, 28.3mg)—In week 6, the formation of the nose, jaw, palate, and lung buds occurs. The fingers and toes form, but may still be webbed. The tail is receding, and the heart is almost fully developed.

Teratogens at this point may leave the fetus with profound heart problems or a cleft lip.

**Week 7** (22.2 mm, 93.5mg)—In week 7, the eyes move forward on the face, and the eyelids and tongue begin to form. All essential organs begin to form (Fig. 4).

Teratogens may cause heart and lung problems, a cleft palate, and ambiguous genitalia (not quite clear male or female).

**Week 8** (25.4 mm, 1.8 g)—The embryo now resembles a human being. The facial features continue to develop and the external ear and the external genitalia appear. By now, the circulation through the umbilical cord is well developed. The long bones begin to form and the muscles are able to contract.

Teratogens may still cause heart problems and stunting of the fingers and toes.

### The Fetus

At this point, the embryo is developed enough to call a fetus. All organs and structures found in a full-term newborn are present.

**Weeks 9 to 12** (76.2 mm, 28.35 g)—The head comprises nearly half of the fetus size and the face is well formed. The eyelids close now and will not reopen until about the 28th week. The tooth buds appear. The genitalia are now clearly visible which indicate the fetus is male or female.

**Weeks 13 to 16** (15.2 cm)—These weeks mark the beginning of the second trimester. Although the skin of the fetus is almost transparent, fine hair develops on the head called lanugo. The fetus makes active movements, including sucking, which leads to some swallowing of the amniotic fluid. A thin dark substance called meconium is made in the intestinal tract. The heart beats 120 to 150 times per minute and brain waves are detectable.

**Weeks 17 to 20** (20.3 cm, 500 g)—Eyebrows and lashes appear and nails appear on fingers and toes. This is an exciting time for the parents: The mother can feel the fetus moving (“quicken”) and the fetal heartbeat can be heard with a stethoscope.

**Weeks 21 to 24** (28.4 cm, 766 g)—All the eye components are developed, footprints and fingerprints are formed, and the entire body is covered in cream-cheese-like vernix caseosa. The fetus now has a startle reflex.

**Weeks 25 to 28** (37.5 cm, 1.2 kg)—This period is the third trimester. During these weeks, rapid brain development occurs. The nervous system is developed enough to control some body functions, and the eyelids open and close. A baby

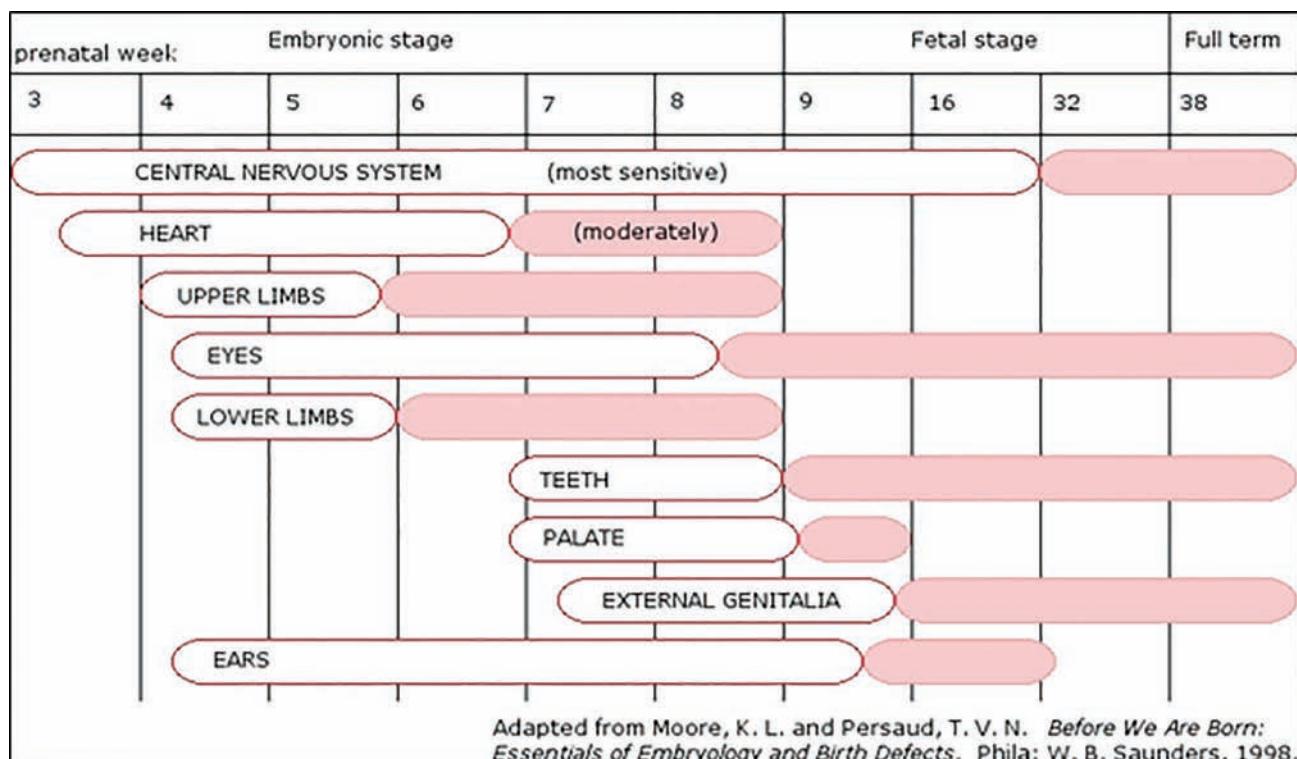


Fig. 4 Timing of birth defects.

born at this time may survive, but the chances of complications and death are high.

**Weeks 29 to 32** (37.5 cm–43.1 cm, 1.9 kg)—These weeks see further development toward independent life: There is a rapid increase in the amount of body fat and the fetus begins storing its own iron, calcium, and phosphorus. The bones are fully developed, but still soft and pliable. There are rhythmic breathing movements present, the fetal body temperature is partially self-controlled, and there is increased central nervous system control over body functions.

**Weeks 33 to 36** (40.6–48.2 cm, 2.6–3.1 kg)—The lanugo (body hair) begins to disappear. A baby born at 36 weeks has a high chance of survival.

**Weeks 37 to 40** (48.2–53.3 cm, 3.1–3.6 kg)—At 38 weeks, the fetus is considered full term. It fills the entire uterus, and its head is the same size around as its shoulders. The mother supplies the fetus with the antibodies it needs to protect it against disease.

## Pre- and Periconceptional Period

Euglycemia is critical during the fertilization. During in vitro development, oocytes and zygotes cultured briefly in the absence of glucose are unable to complete embryo compactions, failing to progress beyond the morula stage.<sup>8</sup> Hyperglycemia culture conditions are also toxic to embryos, indicating that normal development requires a narrow glucose concentration range.<sup>4,9</sup> The ideal glycemic levels during preconceptional period and pregnancy are fasting blood glucose of  $3.9 \pm 0.4 \text{ mmol/L}$  ( $71 \pm 8 \text{ mg/dL}$ ), 1-hour postprandial

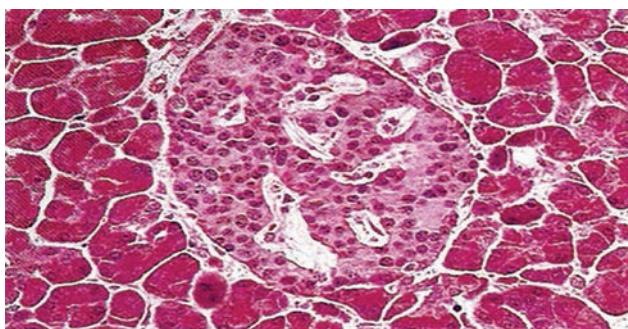
glucose of  $6.0 \pm 0.72 \text{ mmol/L}$  ( $109 \pm 13 \text{ mg/dL}$ ), 2-hour post-prandial glucose of  $5.5 \pm 0.55 \text{ mmol/L}$  ( $99 \pm 10 \text{ mg/dL}$ ), and 24 hours mean of  $4.9 \pm 0.55 \text{ mmol/L}$  ( $88 \pm 10 \text{ mg/dL}$ ).<sup>10</sup>

## Factors Operating in Organ Development and Fetal Growth

The ovum is well supplied with mitochondria, but the sperm contains a few and even those few do not persist in the offspring. At fertilization, it is only the nucleus of the spermatozoa that enters the ovum and thus all the cytoplasm, mitochondria, and mitochondrial DNA are exclusively maternally inherited.<sup>11</sup> Maternal inheritance is attributed to mutation in the gene(s) present on mitochondrial (mt) DNA and is transmitted invariably by an affected mother to her progeny. The unique feature of mitochondrial (mt) DNA is its maternal inheritance.<sup>11</sup>

## Maternal Hyperglycemia and Progeny

Exposure to a diabetic environment in utero is associated with increased occurrence of impaired glucose tolerance and a defective insulin secretary response in adult offsprings, independent of genetic predisposition to type 2 diabetes.<sup>12</sup> This fact is established in Pima Indians. The offsprings of Pima Indians who were in utero when their mother had diabetes have a greater risk of diabetes than earlier siblings born before the mother developed diabetes.<sup>13</sup> “Intrauterine milieu> Inherited Destiny.”



**Fig. 5** Islet cells development. (Adopted from Pancreas Histology, Endocrine, Pancreas Development.)

## Maternal Diabetes and Fetal Insulin Secretion

Fetal pancreas: Each islet cell functions as an endocrine organ. It appears at 11th (►Fig. 5) week of gestation, recognizes and responds to maternal glycemia at 15 to 16 weeks of gestation.<sup>14</sup> Human studies have shown an increase in pancreatic  $\beta$ -cell mass and insulin secretion in the fetuses of poorly controlled diabetic women by 16 weeks gestation.<sup>15</sup>

## Influence of Maternal Hyperglycemia on Fetal Growth

Early maternal metabolic imprinting may affect fetal growth. The priming of the  $\beta$ -cell mass in mid-gestation may account for the persistence of fetal hyperinsulinemia throughout pregnancy and the risk of accelerated fetal growth even when mother enjoys good metabolic control in later pregnancy. Early maternal metabolic imprinting may affect fetal growth.<sup>16,17</sup>

## Importance of First Trimester

The first trimester begins on the first day of the last period and lasts until the end of week 12. This means that by the time one knows for sure of her pregnancy, she might already be 5 or 6 weeks of pregnancy. A lot happens during the first 3 months.

Early gestation exposure to excess maternal fuels may impact the placental transport in a time dependent manner. This results in different growth pattern emphasizing that “earlier intervention” may be important.<sup>3</sup> Though the fetal development is discussed in days and weeks, it is wiser to test the maternal glucose level on the next day woman misses her period. Very early diagnosis of pregnancy can be made by estimating serum  $\beta$ -hydroxy chorionic gonadotropin ( $\beta$ -HCG) at the end of 3rd week of menstrual cycle and by urine  $\beta$ -HCG by the end of 4th week of menstrual cycle.

## Rational for Early Weeks Screening

Metabolic perturbations are underway before the usual diagnosis (24th–28th week) and that earlier screening and intervention may be warranted.<sup>18</sup> Maegawa et al observed (63.6%)

in the first trimester and the rest (36.4%) in the second and third trimesters. This finding suggests the importance of screening for glucose intolerance in the first trimester.<sup>19</sup> Seshiah et al also documented that GDM manifests in all trimesters of pregnancy.<sup>20</sup> Hence, the present concept is that there is a “Need for testing glucose tolerance in the early weeks of pregnancy.”<sup>21</sup> The diagnostic procedure recommended by Diabetes in Pregnancy Study Group India is “A Single Test Procedure.”<sup>22</sup> This procedure is approved by the Ministry of Health and Family Welfare Government of India<sup>23</sup> and is also recognized by World Health Organization (WHO),<sup>24</sup> International Federation of Gynecology and Obstetrics (FIGO),<sup>25</sup> and International Diabetes Federation (IDF).<sup>26</sup>

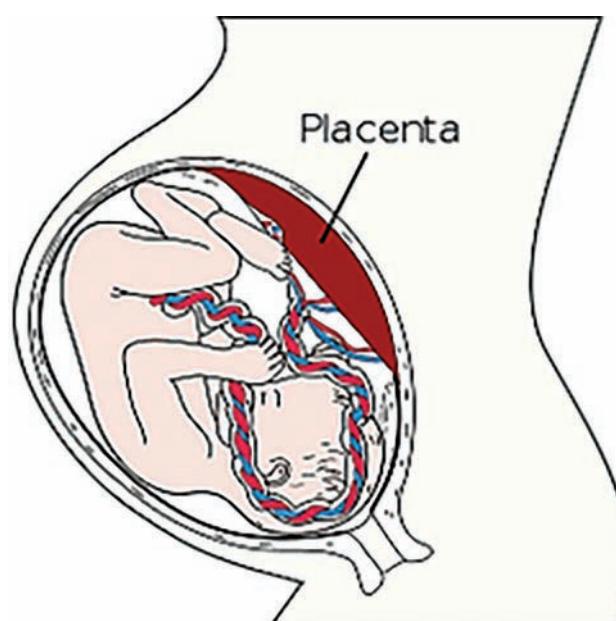
## Advantages of Early Testing

Early testing for glucose intolerance and care could avoid some diabetes-related complications such as hydramnios, fetal anomalies, macrosomia, and preterm births in women with gestational diabetes mellitus.<sup>20,27</sup>

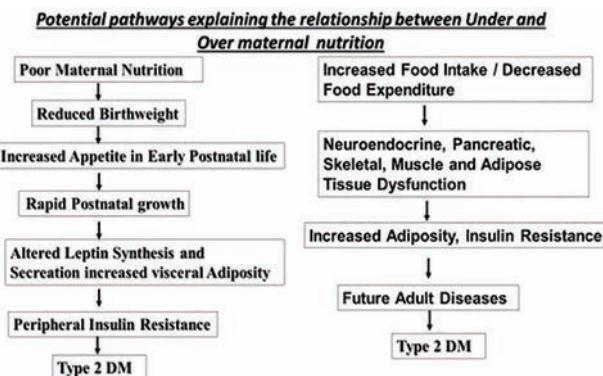
Studies have shown glucose levels at weeks 10 to 14 were positively associated with estimated fetal weight starting at week 23 and the association becomes significant at week 27. Higher glucose concentration in early pregnancy was significantly related to a larger fetal size in late pregnancy.<sup>28</sup>

## Maternal Nutrition and Target for Glycemic Control

The goal of nutrition in pregnancy is to support maternal, placental, and fetal metabolic needs, and it may be the first introduction to a lifetime of healthy eating.<sup>29</sup> Postprandial hyperglycemia plays a more important role in causing fetal overgrowth. Data suggests that postprandial glucose levels more closely relate to macrosomia risk compared with fasting glucose levels.<sup>30,31</sup> Based on studies in preterm births, renal threshold for glucose in the fetus is probably <110 mg/dL.



**Fig. 6** Placentae. (Adopted from Wikipedia, The Free Encyclopaedia.)



**Fig. 7** Effect of maternal nutrition on offspring.

When maternal glucose level is  $>110$  mg/dL, the fetal blood glucose load causes fetal glycosuria and consequently a glucose-enriched amniotic fluid. After 20 weeks of gestation, the fetus begins to swallow the amniotic fluid. In addition to the placental transfer of glucose, ingested high glucose amniotic fluid also stimulates insulin secretion. Thus, even transient elevations of blood glucose on the maternal side not only result in elevations of blood glucose on the fetal side but also provide for glucose ingestion by the fetus for many hours. Thus, postprandial hyperglycemia for less than 1 hour once a day in the mother may produce fetal insulin stimulus, through the oral route for hours. Elevations of maternal glucose levels more frequently (after every meal, for example) may produce a more prolonged oral glucose load for the fetus resulting in an overfed fat fetus.<sup>32</sup> Monitoring maternal glycemia and maintaining 2 hours postprandial plasma glucose between 110 to 120 mg/dL by using plasma calibrated glucometer level every week may be a wise decision.

### Placenta: A Temporary Endocrine Organ

Placenta connects the developing fetus via the umbilical cord to the uterine wall to allow nutrient uptake, thermoregulation, waste elimination, and gas exchange via the mother's blood supply to fight against internal infection and to produce hormones (hyperglycemic—antiinsulin) that support pregnancy.<sup>33</sup> Nutrients pass through it but insulin does not cross and maternal insulin is being destroyed by placental insulinase (**►Fig. 6**).

### Maternal Nutritional Status and Its Influence on the Offspring

The intrauterine milieu is a strong modulator of changes in the pancreatic development and peripheral insulin response. This ultimately culminates in adult onset GDM and T2 diabetes mellitus. Absolute nutritional deviations from the optimum, whether over- or undernutrition, produce the same effect on the offspring<sup>34</sup> (**►Fig. 7**). There is a great variability in fetal growth in the human, based on both genetics and environmental factors. Although we cannot control our genes (with the possible exception of epigenetic phenomena), we may be able to affect fetal growth through alteration in the maternal environment.<sup>35</sup>

## Conclusion

Fetal development invariably involves exquisite interplay between maternal physiology, metabolism, and hormones. Nature nurtures the embryogenesis from conception to confinement. The environment that the oocyte is exposed to during the periconception period can have a significant impact on oocyte developmental competence (the ability of the oocyte to support fertilization and subsequent embryo development) and the long-term health of the resulting offspring. It is necessary to optimize metabolic control early in pregnancy. This will necessitate prepregnancy planning for women with preexisting diabetes, as well as for those at increased risk of GDM, and better means to safely normalize glycemia. Though the fetal development is discussed in days and weeks, it is wiser to test the maternal glucose in the periconceptional period. Monitoring maternal glycemic level every week may be cumbersome but prudent.

### Conflict of Interest

None declared.

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