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Review Article

Evolutionary interactions between diabetes and development

R.G. Ahmed *

Department of Zoology, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt

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ABSTRACT

Because of the complications of diabetes affecting the mothers and their fetus/newborns are less known, this review examined the epidemiologic and mechanistic issues involved in the developmental programming of diabetic mothers. This overview showed that sperm, egg, zygote or blastocyst derived from diabetic parents may develop into offspring with high risk of any type of diabetes, even if placed in a normal uterus, producing developmental delay, embryopathy, geno- and cyto-toxicity, teratogenic changes, free radicals and apoptosis. These early insults may then lead to an increased rate of miscarriage and congenital anomalies depending on free radicals signaling and cell-death pathways involved by the diabetogenic agents. Furthermore, sperm, egg, zygote or blastocyst from normal parents will have an increased risk of diabetes if placed in a diabetic uterus. Interestingly, diabetes has deleterious effect on male/female reproductive functions and on the development of the blastocysts/embryos. Indeed, this review hypothesized that the long-term effects of diabetes during the pregnancy (gestational diabetes) may influence, generally, on the health of the embryos, newborns (perinatal life) and adulthood. However, there are obvious species differences between pregnant women and animal models. Thus, maintaining normoglycaemia during pregnancy may play an important role in a healthy life for the newborns.

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* Tel.: +2 082 2310 187.
E-mail addresses: ragabb900@yahoo.com, r_g_a_ahmed@yahoo.com.
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1. Introduction

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by hyperglycaemia resulting from defective insulin secretion, resistance to insulin action or both [88,228]. In addition, DM is a chronic metabolic disorder triggered by absolute or relative insulin deficiency [123]. Diabetes type 1 is the consequence of an autoimmune-mediated destruction of pancreatic beta cells, leading to insulin deficiency [4]. Both increased insulin resistance and impaired insulin secretion are characterized the type 2 of diabetes [34]. DM type 2 usually occurs in obese individuals and is associated with hypertension and dyslipidaemia [4]. Work with diabetic animal models has demonstrated uterine atrophy [203], reduced mating ability [118,96], alterations of the hypothalamic–hypophysial–ovarian axis [15,16] and, generally, some reproductive problems [173,20]. Also, diabetic animals ovulate at a lower rate than animals with normal glucose levels [46,105,155]. Thus, the general summary about the general effect of both types of diabetes on the pregnancy and perinatal life is shown in Table 1.

Pregnancy cause's insulin resistance and suppresses the intracellular transport of glucose and increases blood glucose concentrations in human [131] and in canines [107]. As well as its role in glucose homeostasis, insulin is an important prenatal and postnatal growth factor through its role in promoting fat deposition and the regulation of the hepatic production of insulin like growth factor 1 (IGF-I) and insulin like growth factor binding protein 1 (IGFBP-1) [19]. Infants born with insulin deficiency [186] or severe insulin resistance [169] are growth retarded with reduced adiposity and persisting reductions in weight gain and growth. Furthermore, congenital malformations are more common in infants of diabetic women than in

Table 1 – The effect of different types of diabetes mellitus on the pregnancy and perinatal life.

Compare face	Diabetes type 1	Diabetes type 2
(1) Define	- It is the consequence of an autoimmune-mediated destruction of pancreatic beta cells, leading to insulin deficiency [4].	- It is characterized by both increased insulin resistance and impaired insulin secretion [34].
(2) Lesions and symptoms	- It causes several lesions in ovarian function [87]; altered ovarian steroidogenesis [11] and an increased incidence of atresia [43]. - It inhibits or retards primordial to primary follicle transition [38]. - It causes some reproductive problems such as spontaneous abortions, neonatal morbidity and mortality, and congenital malformations [20].	- It causes severe hypertension and dyslipidaemia [4,102]. - Women with DM 2 differ from women with DM 1 in several aspects: they tend to be older, more obese, have higher parity, and usually demonstrate less tight glycemic control, each of these being an independent risk factor for perinatal mortality [102].
(3) Congenital anomalies	- These anomalies in their pregnancies were lower than DM 2 [42].	- These anomalies in their pregnancies were more than (doubled) DM 1 [42].
(4) Preconception care	- Their women were more likely to undergo preconception care and were characterized by a higher degree of glycemic control during pregnancy [129].	- Their women were less likely to undergo preconception care (24% vs 48%) and were characterized by a lower degree of glycemic control during pregnancy [129].
(5) Neonatal mortality rates	- In the French study [25], DM 1 was associated with a significantly lower rate of neonatal mortality compared with DM 2.	- In the French study [25], DM 2 was associated with a significantly higher rate of neonatal mortality (7–fold) but with a lower rate of stillbirth compared with DM 1.
(6) Fetal/perinatal death rates	- The rates of perinatal death and late fetal death were almost 4 times and 7 times lower in DM 1 than DM 2, respectively [48].	- The rates of perinatal death and late fetal death were almost 4 times and 7 times higher in DM 2 than DM 1, respectively [48].
(7) Perinatal mortality (PNM) rates	- These rates in their pregnancies were lower than DM 2 [129].	- These rates in their pregnancies were higher than DM 1 [129].
(8) Requirement and control	- Their patients require insulin treatment for survival [4].	- It is controlled by diet and oral hypoglycemic agents prior to pregnancy [129].

children of nondiabetic women [71]. On the other hand, several experimental studies have suggested that the teratological impact of a diabetic environment partly depends on the reactive oxygen species (ROS) in the embryo or the capacity of ROS-scavenging enzymes, or both [72,73,194,227,229,214,71]. As well, oxidant stress associated with insulin resistance and non-insulin-dependent diabetes mellitus [90,138] contributes to poor insulin action [145,79,171].

Animal experiments have contributed much to our understanding of mechanisms of disease, but their value in predicting the effectiveness of treatment strategies in clinical trials has remained controversial [128,167,93,92,146]. In fact, clinical trials are essential because animal studies do not predict with sufficient certainty what will happen in humans [209]. Herein, evolutionary interactions between diabetes and development reviews the epidemiologic and mechanistic issues that exist between a diabetic environment and the malalterations that can occur at various developmental stages: from spermatogenesis and oogenesis to perinatal to metabolic programming in fetal/child that lead to metabolic syndrome in adulthood. The goal of this paper is to establish from clinical studies and experimental models a review in support of a working hypothesis that glycemic control during pre-gestational and pregnancy plays a key role in the developmental processes and may work against the evolution of diabetes.

2. Diabetogenic agents

Streptozotocin (STZ) and alloxan (AL) are pancreatic β-cell selective toxins that have been extensively used to probe the mechanisms underlying oxygen-mediated damage to rodent β-cells. Both of these diabetogens reduce the level of nicotinamide adenine dinucleotide in pancreatic islets and inhibit proinsulin synthesis [225,176,126]. The ROS, produced by AL and STZ, mediate β-cell necrosis and a permanent insulin-dependent DM syndrome [126].

2.1. *Streptozotocin (STZ)*

DM by STZ is a degenerative disease that has deleterious effects on male reproductive function [162,7], on oocyte development [38] and on the development of the embryo, particularly the metabolic and signaling systems [17,73,217,86]. The mechanisms by which STZ induces diabetes are not clearly understood [4]. Oxygen free radicals, including hydroxyl radicals, have been suggested to be involved in the toxic action of STZ [47,202,140,4]. STZ is a chemically unstable molecule that accumulates in pancreatic beta cells [182] and produces toxic radicals during its decay [4]. Highly reactive carbonium radicals originating from the decay of STZ molecules might increase the production of oxygen free radicals [47]. These highly reactive radicals exert direct or indirect toxic effects on islet endothelium [70] and mediate fragmentation of nuclear DNA in beta cells [225,202]. It is also found that STZ, at low dose, damages pancreatic beta cells by eliciting non-specific islet inflammation with infiltration by mononuclear cells [121]. Nitric oxide generated by STZ has been proposed to be involved in the damage of pancreatic beta cells [109,6,4].

On the other hand, STZ is a potent alkylating agent known to directly methylate DNA and is highly genotoxic, producing DNA strand breaks [149,181,115,137], alkali-labile sites and DNA adducts [26], unscheduled DNA synthesis [184,82], all types of chromosomal aberrations [85,221,197,108,28,27], and cell death [135,175,94]. Particularly, the mechanism of STZ-induced hyperglycemia is considered as follows; STZ causes DNA strand breaks in pancreatic islets and stimulates nuclear poly(ADP-ribose) synthetase, and thus depletes the intracellular NAD and NADP levels (3–6) [140]. The genotoxic effects of STZ indicates that this compound induces DNA damage by alkylation of specific sites on DNA bases and that free radicals generated during STZ metabolization seems to play a significant role in the mechanism of DNA damage and cytotoxicity by STZ [26]. Also, The mutagenic activity of STZ in mammalian systems was demonstrated in rats (1 or 10 mg/kg bw), in mice (400 μg per mouse) [83] and in V79 cells of Chinese hamster [24]. Moreover, STZ was found to be carcinogenic in rats, mice and hamster [23,213,158,104,185,166].

To our knowledge, data on the carcinogenic effects of STZ in humans are still unavailable. None of the existing reports published regarding the clinical use of STZ alone or in combination with other antineoplastic agents indicates secondary drug-induced tumorigenesis [205,215,41,165]. As the International Agency for Research on Cancer [103] emphasizes, STZ should be regarded for practical purposes as it were carcinogenic to humans. Accordingly, STZ is classified by the IARC within Group 2B (The agent (mixture) is possibly carcinogenic to humans. At present, the clinical use of STZ is very limited due to the development of resistance of human tumor cells and the severe toxicity and myelosuppression induced by the antibiotic [26,27]. A more intensive work needs to be done regarding the mechanisms that confer resistance to STZ and the factors that can reduce the toxic effects of STZ on human subjects for this drug to become an effective antineoplastic agent.

2.2. *Alloxan (AL)*

AL is a pyrimidine derivative compound (2,4,5,6-tetraoxypyrimidine 5,6-dioxyuracil) and a good inducer of diabetes in experimental models [63,14,117,136]. A different dose of AL changes the hypothalamic–hypophysial–ovarian axis in prepubertal (35-d-old) rats [101] and causes mating failure, litters with dead neonates, cannibalism [193,144], fetal resorptions [65] and maternal death or pregnancy loss [193,10,144]. Also, AL decreases the testis weight and testosterone level, and inhibits the spermatogenesis process [183]. Thus, this review suggests that AL-induced diabetes may cause a delay of development or embryotoxicity depending on the dose, duration and rout of AL-injection and developmental period.

On the other hand, ROS generation mediates AL cytotoxicity [91,69] when it comes in contact with suitable thiols, typically the tripeptide glutathione (GSH) [9,222]. AL-induced cell damage has been attributed to the production of toxic superoxide anion, hydroxyl radicals and hydrogen peroxide [66]. Also, the selective cytotoxicity of AL to the pancreatic beta cell is attributable to the conjunction of two features: a rapid cellular uptake of the drug and an exquisite sensitivity of the beta cell to peroxide [125]. Furthermore, AL caused DNA strand

breaks to stimulate nuclear poly(ADP-ribose) synthetase, thereby depleting intracellular NAD level and inhibiting proinsulin synthesis [225,207,136]. Actually, islet DNA strand breaks were observed *in vivo* by administration of AL to rats [226,136]. The exact mechanism of DNA damage induced by AL remains to be clarified, although various possible mechanisms have been proposed.

Despite the above, an adequate experimental model is unavailable for the study of the *in vivo* diabetes–development (gestation) interaction, since there are controversies on both the time of induction and the amount and route of the diabetogenic substance (STZ or AL) injected, as well as its effects on embryo and fetal development.

3. Diabetes and spermatogenesis interactions

DM has deleterious effects on male reproductive function, possibly through an increase in oxidative stress [106,162,7]. About 90% of diabetic patients have disturbances in sexual function, including a decrease in libido, impotence and infertility, in the latter case due to testicular dysfunction associated with sustained hyperglycaemia [32,106]. Also, in patients with a severe type of DM, higher percentage of immobile and pathological types of spermatozoa was recorded [114]. However, the mechanisms of altered spermatogenesis in diabetic men are poorly understood. Also, the experimental induction of DM in animal models using chemical diabetogens is demonstrated to impair testicular function progressively leading to decreased fertility [188]. The reduction in sperm concentration and motility and impairment in mating behaviour and sperm ejaculation were found in Goto-Kakizaki (GK) rats treated with STZ [96,172]. Furthermore, Soudamani et al. also found that STZ induced diabetes has detrimental effects on the maintenance and establishment of fully differentiated epididymal epithelium during sexual maturation [196]. Since Ref. [7] found no differences in testicular cell concentration between different groups, the decrease in sperm concentration is likely due to the influence of severe hyperglycaemia in late stages of spermatogenesis, possibly through an increase in ROS. The consequences of such oxidative damage could include loss of motility due lipid peroxidation [190,5] and induction of DNA damage in the sperm nucleus [5]. From the above findings, it can infer that DM may cause errors in spermiogenesis affecting fertilizing potential.

While the role of oxidative stress in the development of various diabetic complications is well known [18], the involvement of oxidative stress mechanisms and their contribution in the development of testicular dysfunctions under diabetes is poorly understood. Cai et al. [31] and Unlucerci et al. [208] recorded the occurrence of oxidative impairments in testis and genotoxic effects in male germ cells of diabetic rats administered STZ. However, studies on the progression of oxidative damage, its impact on sperm morphology/development in STZ-diabetic mice is totally lacking. Accordingly, STZ induces oxidative damage in testicular and epididymal milieu in mice during the early diabetic phase [188]. This assumes relevance since elevated oxidative stress in the testicular milieu is demonstrated to have profound implications on testicular physiology and sperm function [3,54,2,1,159]. Hence, even slight alterations in ROS levels and their detoxification can substantially affect the spermatogenetic process since germ cells are more susceptible to peroxidative damage [98]. Based on the occurrence of oxidative impairments in STZ-treated mice during both early and progressive phase, it is hypothesized that oxidative stress mechanisms may be wholly or in part contribute towards the development of testicular dysfunction and degeneration under situations of experimentally induced diabetes in animal models [188]. DM and insulin resistance affect semen parameters and impair distinct phases of spermatogenesis in male rats [12]. Animals with diabetes that did not receive insulin exhibited extensive spermatogenic disruption [89].

Furthermore, results of Ref. [12] suggested the following mechanisms in the impairment of spermatogenesis by DM: (1) Disturbance in the functions of sertoli cells with or without a disturbance or disruption in the physiology and/or morphology of the blood–tesis barrier [170,139]; (2) Alterations in the microenvironment provided by the sertoli cells, either directly or resulting from changes in paracrine signals from the seminiferous tubules [143]; and (3) Disruption of ionic channels [164]. Taken together, these results allow me to conclude that DM has adverse effects in energy levels, sperm concentration and sperm motility in men or animal model. In general, the reproductive dysfunctions both structurally and functionally may occur during the conditions of DM. Additional studies are warranted in large scale to confirm the beneficial effect of insulin on fecundity.

4. Diabetes and oogenesis interactions

Ovarian follicular development and growth are controlled by pituitary gonadotrophins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and by local factors, such as steroid hormones and growth factors [187]. Among endocrine factors, insulin and growth hormone (GH), metabolism-related factors, are also crucial factors for follicular development in the mammalian ovary [187]. Circulating insulin concentrations exhibit diurnal variation, but also change during the estrous cycle, with significantly increased concentrations during the preovulatory period [127,13]. Such insulin action is mediated through the insulin receptor, which first appears in granulosa cells of preantral follicles [177,220]. Also, Ref. [200] revealed exogenous insulin administration did not affect the follicle population but has shown favourable effect on large follicle diameter. Thus, the beneficial effect of insulin on ovulation rate might be due to either increase in follicle recruitment or rescuing follicles from atresia [200]. Insulin receptors (IRs) are widely distributed throughout all ovarian compartments, including granulosa, thecal and stromal tissue [152,151,153,67,68]. Previous studies from Ref. [111] have shown that insulin acts as a paracrine factor to facilitate transition from primordial to primary follicle at the level of the oocyte. In other studies, Ref. [50] has shown that IGF-I has a stimulatory effect on follicular steroidogenesis and improved the quality of the oocyte and embryo development. Other studies have suggested that IGF-I

and insulin enhance granulosa cell proliferation and increase follicle diameter [230].

A combination between acute and long-term diabetes by using STZ and genetic Akita mice caused significant delays in germinal vesicle breakdown (GVB) and resumption of meiosis I [38]. Indeed, Ref. [51] has reported that meiotic resumption is attenuated in superovulated diabetic mice. Varying the relative amounts of glucose and pyruvate can either induce or impede GVB in cumulus cell-enclosed oocytes in the presence of meiotic inhibitors such as hypoxanthine or dibutyryl cAMP (dbcAMP); glucose provides an inhibitory influence when high levels of pyruvate are present yet is required for hormone-induced maturation [55,56]. Evidence suggests that the glycolytic pathway mediates the inhibitory action of glucose through the generation of adenosine triphosphate (ATP) [55,57], and the positive action of glucose requires the participation of the pentose phosphate pathway [58–60]. Both the meiosis-inducing and -suppressing effects of glucose on oocyte maturation appear to be mediated by the gap junctional communication pathway that metabolically couples the oocyte with the somatic compartment of the follicle [77,57,61]. Moreover, the delay in FSH-stimulated oocyte maturation experienced by the STZ-induced diabetic mice could be only partially recreated *in vitro* with high-glucose conditions, suggesting other factors may be involved [43]. Whether the diabetic state influenced granulosa cell intercellular communication? It is possible that the maturational delay suspected in oocytes from diabetic mice will be a result of poor paracrine communication between these two compartments because of poor intercellular talk among granulosa cells [38]. Colton et al. demonstrated a loss of metabolic communication between granulosa cells and oocytes in cumulus-enclosed oocytes (CEOs) from diabetic mice [44]. Colton et al. [43] hypothesized that maternal diabetes would have a detrimental effect on oocyte maturation and that the follicular environment of the enclosed cumulus complex and oocyte immediately after human chorionic gonadotropin (hCG) administration would be adversely affected. It is hypothesized that an insult or a preprogramming event may occur at the oocyte stage secondary to maternal hyperglycaemia that permanently alters the course of normal development, and this manifests first as a maturational delay. Therefore, there is evidence that oocyte-directed insults may be the result of poorly controlled diabetes during folliculogenesis in animal models as well as humans and that these insults may result in later reproductive failures, such as a higher incidence of malformation and miscarriages in this population of patients.

In addition, Chang et al. [38] speculated that the follicles and oocytes at all stages of development in Akita mice are smaller compared with the follicles from the control animals and these may reflect the abnormal cell growth and survival, which would correlate with the increased apoptosis seen in the CEOs from the diabetic mice. Similarly, several studies in human oocytes have correlated small oocyte size with poorer developmental potential and pregnancy rates [22,206]. It is observed from the above mentioned results that diabetic animals or women who experience uncontrolled or poorly controlled diabetes during ovulation may suffer detrimental effects on follicles or oocytes and then on fertilization and development. Collectively, the reduction in ovulation rate may be due to several causes as a following: (1) A defect in the blood–follicle barrier in diabetic mice as indicated by a delay in the hCG-stimulated influx of the serum glycoprotein, inter-α-inhibitor, that is associated with a deficit in superoxide dismutase activity [155]; (2) Failure to protect nitric oxide, which is an important regulator of this process [189,156]; (3) A defect in the hypothalamic–ovarian axis, a suppressed LH surge, altered ovarian steroidogenesis, or a decrease in hormone-binding responsiveness [46,11,105,155]; (4) A significant reduction in metabolic coupling was demonstrated in complexes from diabetic mice [204]; and (5) AMP-activated protein kinase (AMPK) activity is decreased in the oocyte complex in response to the diabetic condition, as has been described in other tissues exposed to a diabetic milieu [15,16,81].

Furthermore, Colton et al. [44] shown that the type 1 diabetic condition significantly alters meiotic regulation in mouse oocytes. Since glucose can play different roles in the meiotic maturation of isolated oocytes, it was important to assess how a diabetic environment would influence oocyte maturation. It is apparent from the pre-said studies that meiotic resumption is adversely affected in oocytes from diabetic animals, which may impact negatively on subsequent developmental capacity. My rationale is that, if the corrections of these abnormalities in ova will achieve before the division (in preantral follicles), the defect in meiotic maturation may reverse and perhaps improve pregnancy outcomes in these conditions. Concurrently, these data are therefore consistent with the idea that diabetic conditions during oogenesis and oocyte maturation have a detrimental impact on later development and that continual exposure to elevated glucose following fertilization further compounds this problem.

5. Gestational diabetes (GDM)

Whereas gestational DM reflects decreased ability to utilize glucose, pregnancy also decreases the ability to produce glucose via gluconeogenesis, glycogenolysis and lipolysis, because the normal glucagon, norepinephrine, and cortisol responses to hypoglycemia are blunted late in pregnancy [45,33]. This decreased ability to produce glucose, combined with the increased utilization of glucose by the placenta and fetus, create a risk of developing hypoglycemia [107]. The latter author said that despite similar findings of low plasma insulin concentrations and suppressed glucose production in pregnant women, sheep and dogs, there are marked species differences in the conditions called ''pregnancy toxemia''. In sheep, glucose homeostasis is less well controlled during late pregnancy than during early lactation, despite the significantly higher glucose turnover during lactation than during late gestation [179,180]. Also, in pregnant sheep, ketone body utilization is impaired during late pregnancy, which aggravates the hyperketonemia [95]. Hyperketonemia itself inhibits hepatic glucose production, which aggravates the hypoglycemia and hypocalcemia causes a decrease in plasma glucose concentrations in pregnant, as well as in lactating and non-pregnant (non-lactating sheep) [107]. In ovine, the primary cause of pregnancy toxemia is a reduction in glucose production, rather than the increased utilization by the fetus and placenta [180]. In

dairy cattle, hypoglycemia and ketosis develop during the immediate postpartum period and at peak lactation [99].

In women, the term "pregnancy toxemia" refers to preeclampsia. It occurs in 5–7% of human pregnancies [211,97]. Preeclampsia is a multisystemic disorder characterized by hypertension and proteinuria after 20 weeks of gestation [195,119,122,211]. Renal failure, stroke, seizures (eclampsia), HELLP syndrome (hemolysis (H), elevated liver tests (EL) and low platelet count (LP)) and death are risks to the mother [107]. The cause(s) of preeclampsia remains unknown, but oxidative stress, inflammation, insulin resistance, obesity, calcium imbalance, genetic factors, and antiangiogenic factors causing endothelial dysfunction may all be involved [107].

6. Perinatal diabetes

Antenatally, insulin is secreted in response to the continuous regulated supply of glucose across the placenta and its primary role is one of promoting growth and fat deposition [19]. Insulin secretion increases during the last trimester of pregnancy and cord blood insulin levels correlate with size at birth [64]. Postnatally, insulin's role in glucose homeostasis becomes paramount, secretion comes under the influence of neural, neuroendocrine and enteroendocrine mechanisms [19], and the insulin secretion is coupled to the enteric supply of milk and release of incretins. Furthermore, abnormal placentation, fetal growth retardation, death and premature delivery are risks to the fetus [107]. However, animal studies have demonstrated a relative lag in insulin secretion in the newborn in response to dextrose infusion with a delayed peak [150], and in humans there has been shown to be disproportionately elevated proinsulin levels [133]. In the perinatal period, there is a transient wave of beta cell apoptosis and beta cell neogenesis associated with hypoinsulinism and this is influenced by the perinatal environment [163]. This apoptosis may occur early postnatally or at weaning [178], and in rats it occurs at the same time as a significant fall in the levels of insulin growth factor 2 (IGF-II) expressions [147], and can be prevented by over expression of IGF-II [148]. Moreover, Ref. [148] appeared that an overexpression of IGF-II in fetal life has a profound effect on islet morphology and causes islet hyperplasia while reducing the attrition of islet cells by apoptosis. Human post-mortem studies show similar evidence of beta cell apoptosis with a new population of beta cells compensating for the perinatal beta cell loss [110]. Also, in humans, this transient insulin deficiency may be reflected in the catabolism and early weight loss observed in all infants [19]. Moreover, diabetic fathers (particularly multiple subdiabetogenic doses (MD) of streptozocin) mated with normal females produced offspring with significantly higher juvenile body weights than the controls (increase of approximately 0.5 g) [199]. These findings strongly suggest that any interference with this process of remodelling may have a critical impact on the ability of the pancreas to meet requirements for insulin secretion in later life. Glucose crosses the placenta and maternal hyperglycaemia during pregnancy results in increased glucose concentrations in the fetus [192]. The latter authors undertook that during pregnancy, in particular under the influence of inappropriately high glucose concentrations, altered brain cells, and later pancreatic beta cells, adipose and muscle cells, and nephron development may occur, leading to long-term consequences throughout life. It can infer that insulin, perhaps of maternal origin, may play important roles in perinatal development. In general, there is a balance between cell replication, neogenesis and apoptosis during fetal life. However, the ontogeny of insulin secretion during fetal and early postnatal life is poorly defined and insulin treatment in the management of preterm infants with hyperglycaemia remains controversial.

7. Maternal teratology, embryopathy and diabetes interactions

Both environmental factors and genetic predisposition seem to be of importance in diabetic embryopathy [71]. Moreover, several teratological pathways have been suggested, often from clinical experience, and subsequently characterized in various experimental systems. In general, the number of different teratogenic agents identified would indicate that diabetic embryopathy is of complex etiology [112,174,30,71]. The maternal teratogenic factors most often indicated are hyperglycaemia [134] and ketonemia [30,142]. Major teratogenic processes in embryonic tissues so far identified include alterations of metabolic and signaling systems such as metabolism of inositol [17], sorbitol [74], arachidonic acid/prostaglandins (PG) [17], folic acid [217], and ROS [73], as well as alterations in the activation of protein kinase C (PKC) isoforms [86]. The embryonic formation of glycated proteins [76], and the maternal and fetal genotypes [37] are also suggested to influence the teratological events in diabetic pregnancy. This part will deal with the teratological impact of diabetes depends on excess of ROS.

Previous experimental studies have suggested that the teratological impact of a diabetic environment partly depends on excess of ROS in the embryo [72] as a consequence of either increased free oxygen radical formation [73,227] or decreased capacity of ROS-scavenging enzymes [194,229,214], or both [71]. If the diabetic state is associated with a generalized increase in oxidative stress, it might well be reflected in the alterations in embryonic and fetal development during pregnancy or causing embryonic death (abortion/miscarriage) [49]. Previous work has also demonstrated that supplementation of antioxidative agents such as copper–zinc superoxide dismutase (SOD) [72,73], N-acetylcysteine (NAC) [218], vitamins E and C [229] and folic acid [217] *in vitro*, as well as butylated hydroxytoluene [75], vitamin E [36,161], vitamin C [36], NAC [168] and folic acid [217] *in vivo* attenuate malformation rate and diminish markers of oxidative stress, e.g. by normalizing tissue levels of thiobarbituric acid-reactive substance (TBARS) [191], isoprostane 8-iso-prostagladin (PG) $F_{2\alpha}$ [219,216] and carbonylated proteins [35]. Moreover, Ref. [72] found that adding scavenging enzymes, e.g. SOD, catalase (CAT) or glutathione peroxidase (GSH-Px), to the culture medium protects rat embryos from dysmorphogenesis induced by high glucose concentration *in vitro*. Teratogenic concentrations of β-hydroxybutyrate or the branched chain amino acid analogue α-ketoisocaproic acid can be blocked by addition of SOD to the culture medium [73], and addition of

Table 2 – Prevention of the diabetic malformations during the development (modified from paper of Ref. [71]).

(1) Inositol supplementation	Supplementation of inositol diminishes embryonic maldevelopment in high-glucose-exposed embryos *in vitro*, as well as in fetuses of diabetic rats. No studies have been performed in human diabetic pregnancy.
(2) Arachidonic acid supplementation	Supplementation of arachidonic acid diminishes embryonic maldevelopment in high-glucose-exposed embryos *in vitro*, as well as in fetuses of diabetic rats. No studies have been performed in human diabetic pregnancy.
(3) Antioxidant supplementation	Supplementation of antioxidants diminishes embryonic maldevelopment in experimental diabetic pregnancy, both *in vivo* and *in vitro*. No studies have been performed in human diabetic pregnancy aiming to diminish embryopathy, but vitamin E (400 IE) and vitamin C (1 g) have been administered to non-diabetic pregnant women from early gestation (week 18–22) and throughout pregnancy in order to prevent pre-eclampsia, however with no significant beneficial effect [154]. Moreover, about 750 pregnant diabetic women have been given this vitamin dose or placebo from early gestation (week 8–22) in the ongoing Diabetes and Pre-eclampsia Intervention Trial (DAPIT), aiming to diminishing pre-eclampsia in diabetic women [100].
(4) Folic acid supplementation	Supplementation of folic acid diminishes embryonic maldevelopment in high-glucose-exposed embryos *in vitro*, as well as in fetuses of diabetic rats. No studies have been performed in human diabetic pregnancy.

SOD or NAC diminishes the dysmorphogenesis caused by diabetic serum [218]. Examination of litters of diabetic rats demonstrated lowered α-tocopherol (vitamin E) concentration in day-11 embryos and in the liver of day-20 fetuses [191]. This suggests that long-term exposure to high glucose creates embryonic ROS excess either from increased ROS production [227], or from diminished antioxidant defense capacity [130]. ROS excess may be relatively small, restricted to particular cell populations [39], and likely to vary with gestational time and nutritional status, making direct ROS determinations difficult. Nevertheless, a cyclic voltametry measurement of oxidation potential in preimplantation rodent embryos cultured in diabetic serum indicated the presence of ROS excess also at this stage [141]. In addition, fetuses and embryos of diabetic rodents displayed increased rates of DNA damage [116]. The driving cellular force behind the diabetes-induced oxidative stress is likely to be associated with the enhanced glucose metabolism [80,120] in the embryonic and fetal cells exposed to the increased ambient levels of glucose. Generally, Ref. [62] revealed that four major molecular mechanisms have been implicated in hyperglycaemia-induced tissue damage: (1) Activation of PKC isoforms via de novo synthesis of the lipid second messenger diacylglycerol; (2) Increased hexosamine pathway flux; (3) Increased advanced glycation end product (AGE) formation; and (4) Increased polyol pathway flux. In addition, it has been shown that all of these mechanisms reflect a single hyperglycaemia-induced process: overproduction of superoxide by the mitochondrial electron transport chain [29]. However, the molecular mechanism by which this hyperglycaemia-induced overproduction of superoxide activates these different pathways of hyperglycemic damage has not been elucidated. According to Ref. [124], antioxidant enzyme-dependent defences may play an important role by scavenging free radicals produced under oxidative stress. It can suppose that any disturbance between antioxidant and ROS due to DM during the pregnancy may lead to severe malformations in the development of the embryo and newborns. Blocking excess ROS activity may constitute an important therapeutic alternative in the future (Table 2) [71]. Thus, the disturbance in the pro/antioxidant system due to the insulin dysfunction may retard the growth. From these findings, this review suggests that oxidative stress occurs in the diabetic pregnant state, which might promote maternal homeostasis alterations. Furthermore, the above results presumed that, the insulin-antioxidant system interactions could protect the cells and tissues, in general, during the development from the harmful effect of ROS due to GDM. Further studies are required to determine if these beneficial effects result in changes of diabetes complications only or not (inherited program modulate them).

Table 3 – Short- and long-range complications of offspring of diabetic mothers [212].

Age at expression	Period of exposure	Complications
Fetus	1st trimester	Early growth delay and congenital anomalies.
	2nd trimester	Macrosomia, organomegaly (selective) and nervous system development delay.
	3rd trimester	Chronic hypoxemia and stillbirth.
Newborn	Delivery	Birth injury, respiratory distress syndrome, hypoglycemia, hypocalcemia, hypomagnesemia, thrombocytopenia, polycythemia or hyperbilirubinemia and hyperviscosity syndrome.
Child/adult		Behavior deficit, behavior intellect deficit and obesity (impaired glucose tolerance and then diabetes mellitus).

Table 4 – Effect of diabetes mellitus on different developmental stages.

(A) Spermatogenesis
Diabetes can cause the following in men or experimental animals
(1) Impairment of spermatogenesis, reduced sperm count, motility, seminal fluid volume, and serum testosterone [198,132,196,8].
(2) Impotency, and loss of libido [196].
(3) Male subfertility (decreased fertility potential) by altering steroidogenesis and sperm motility [188,113].
(4) Testicular and erectile dysfunctions, and retrograde ejaculations [8].
(5) More importantly, diabetes mellitus may induce genotoxic effects during spermatogenesis [188].

(B) Oogenesis
The previous studies on diabetes have revealed that
(1) Delays the growth of preovulatory- and antral-follicles and generally oocyte maturation [38].
(2) Reduced the number of ova ovulated [155,43].
(3) Reduced the cell–cell communication between oocyte and cumulus cells [44].
(4) Increased apoptosis in the surrounding granulosa cells, up-regulation of the extrinsic apoptotic pathway, and diminished levels of a key gap junction protein [38].
(5) Defect in the blood–follicle barrier [155].
(6) Delayed the meiotic maturation of folliculogenesis and subsequent developmental potential [43].
(7) Generally, women with type I diabetes mellitus may be placing their oocytes at risk [38].

(C) Fertilizations
(1) Fertilization rates were significantly lower in the Akita mice group (17.9%) and the streptozotocin (STZ)-injected male group (43.6%) when compared with the normal group (88.8%) [113].
(2) Zygotes removed from STZ – or alloxan (AL)-induced hypoinsulinemic and hyperglycemic mice demonstrate retarded *in vivo* development to a two-cell stage with a lower percentage of two-cell zygotes recovered at 48 h after human chorionic gonadotropin (hCG) compared with nondiabetic controls [51].
(3) Defects in meiotic regulation brought about by the diabetic condition are due to decreased communication between the somatic and germ cell compartments, and it is concluded that such conditions may contribute to postfertilization and developmental abnormalities [43].
(4) It is known from human studies on patients undergoing *in vitro* fertilization that increased cumulus cell apoptosis correlates with poorer-quality oocytes and poor pregnancy outcome including increased rates of miscarriage [38].
(5) Generally, severe hyperglycemia caused errors in spermiogenesis and affecting fertilizing potential [5,7].

(D) Blastocysts
(1) Blastocysts retrieved from diabetic animals typically contain fewer cells than those from nondiabetic control animals [21].
(2) A significant impairment in development was seen in the embryos from diabetic mice in their rates of progression to blastocyst compared with nondiabetic mice, despite the fact that both were cultured in identical medium conditions [51,231].
(3) High glucose alone or combined with high ketone body levels inhibited further development of blastocysts in a dose-dependent manner [43,232].
(4) Interestingly, apoptosis was increased in the blastocysts obtained *in vivo vs.* those cultured *in vitro* in high-glucose conditions, suggesting that this apoptosis may be occurring under the combined influence of both the extrinsic and intrinsic pathways [38].
(5) The damage to the embryo likely occurs early since almost 50% of two-cell embryos isolated from subdiabetic rats were unable to develop to the 8-cell stage, even in a nondiabetic tract [210].

(E) Embryos
(1) High glucose concentrations in embryo culture medium lead to impaired embryo development [52,53]. This effect may be due to downstream metabolic intermediates since developmental retardation *in vitro* is also observed with high concentrations of fructose, sorbitol, or ketone bodies [173,134].
(2) Diabetes has been shown to cause delays in embryonic development [155,43]. In humans, type 1 or insulin-dependent diabetes has been found to negatively affect pregnancy by causing poor prenatal outcomes such as an increased risk of congenital anomalies and early miscarriage [78].
(3) Maternal diabetes has been found to adversely affect murine preimplantation embryo development in models of type 1 diabetes [40,38].
(4) Preimplantation embryos from diabetic mice that, when removed from the diabetic milieu, still experience significant developmental delay and apoptosis by the blastocyst stage [160].
(5) Diabetes-induced inappropriate apoptosis in embryos during neurulation may be one of the mechanisms leading to neural tube defects [201].

(F) Offspring
(1) Generally, women with type I diabetes mellitus may be placing their offspring at risk [38].
(2) Exposure to maternal diabetes during oogenesis, fertilization, and the first 24 h was enough to program permanently the fetus to develop significant morphological changes (adversely affects) [224].
(3) It seems that embryos exposed to a diabetic conditions show pronounced dysmorphogenesis, which may be induced many alterations after the delivery. Embryos recovered *in vivo* at 48 h after fertilization from chemically induced diabetic mice experience an *in vivo* developmental delay [38].

8. General summary about the maternal metabolic aberrations due to DM during pregnancy and a serious impact from fetus to young adult

Short- and long-range complications of offspring of diabetic mothers are presented in Table 3 [212].

9. General summary about the effect of DM on the different developmental stages

Effect of diabetes mellitus on different developmental stages is presented in Table 4 and Fig. 1.

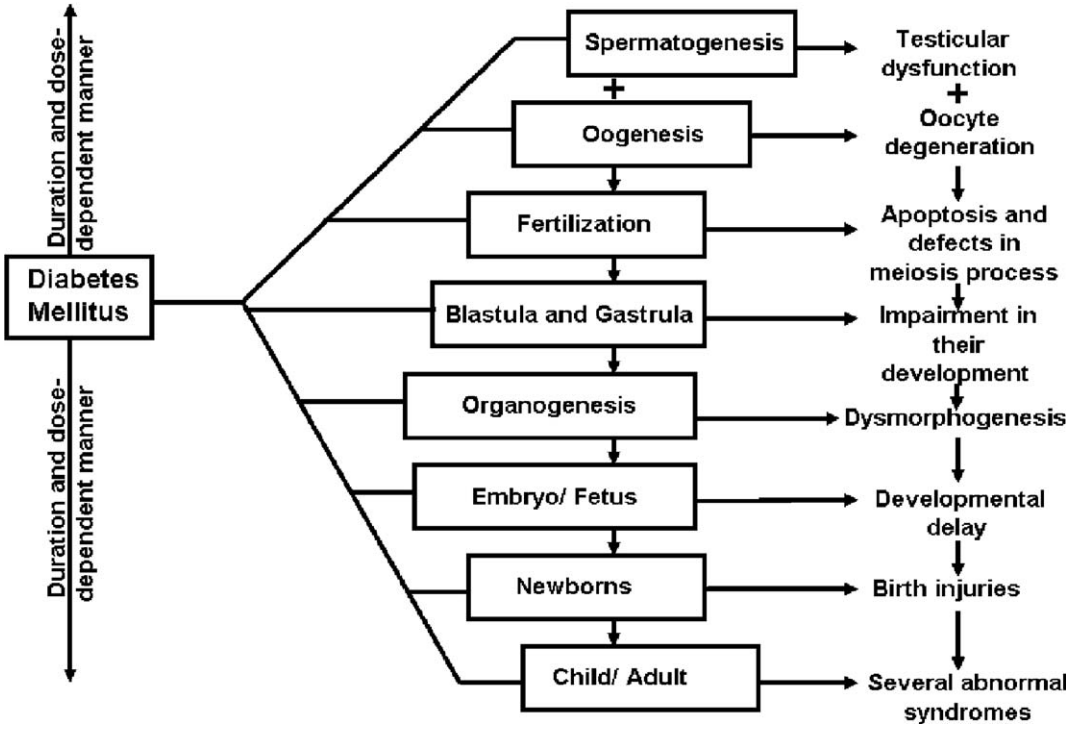

Fig. 1 – Effect of diabetes mellitus on different developmental stages.

10. Recommendation

It is goal to encourage the early referral of both pre-gestational and gestational diabetic women so that tight glycemic control will be instituted at the proper time in order to prevent maternal hyperglycaemia complications [157,223]. At the same time, a better understanding of the physiological, cellular and molecular mechanisms of the developmental programming of hypertension, diabetes type 2 and eventually obesity by in utero exposure to diabetes in pregnancy may unveil pharmacological and nutritional targets for early prevention. The abnormal uterine environment may have deleterious effects on fetal/child metabolic programming and lead to metabolic syndrome in adulthood. A balanced/restricted diet and/or physical exercise often improve metabolic abnormalities in individuals with obesity and type 2 DM. This suggests that an appropriate dietary fatty acid profile and intake during the periconceptual/gestation/lactation period helps the female offspring to cope with deleterious intrauterine conditions [84]. The hypothesis may change the focus from treatment of children and adults to prevention during early development. It also changes the focus from classical genetics to epigenetics and to nutrition and environmental chemical exposures during development; most importantly, it changes the focus from intervention to prevention. Also, antioxidant treatment of women with diabetes may be important in future attempts to prevent congenital malformations [49].

Conflict of interest

There are no conflicts of interest.

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