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# Influences of excess adiposity on reproductive function

TAHIR A MAHMOOD

## Introduction

We are dealing with an obesity pandemic and its consequences. There is a rising incidence of type 2 diabetes mellitus and its concomitant co-morbidities such as cardiovascular disease and polycystic ovarian disease among females of reproductive age. Obesity and its associated abnormal biochemical milieu adversely affect the reproductive function of males and females. Of particular concern is whether these effects will also be more marked in the next generation of newborns, especially those born to mothers who developed GDM.

## Treatment of gestational diabetes: which agent?

GDM is associated with increased perinatal mortality such as macrosomia and shoulder dystocia, thereby increasing the need for surgical intervention in the form of instrumental delivery and Caesarean section. Macrosomia is also associated with an increased risk of intra-uterine death, birth trauma, and neonatal hypoglycaemia. These large for gestational age babies are at increased risk of obesity, metabolic syndrome and type 2 diabetes later in life. The argument is no longer whether GDM should be treated, but by which agent. This hypothesis is supported by the results of the ACHOIS study<sup>1</sup> in which the intervention group had better outcomes than the group managed with diet alone. The MIG study<sup>2</sup> clearly demonstrated that in the management of GDM metformin was as effective as insulin with comparable neonatal morbidity and the risk of developing large for gestational age babies. Reassuringly, women using metformin had reduced weight gain: an average 1.6 kg less than the insulin group. It is also reassuring to note that metformin is not teratogenic and does not adversely affect anthropometric and motor/social development in the first 18 months of life.<sup>3</sup>

In this edition, Hyer *et al.*<sup>4</sup> describe their experience of managing a large cohort of 200 women with GDM. In their series, an equal number of patients were treated with either metformin or with insulin. In the metformin group there was a



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## Abbreviations and acronyms

ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
BMI	body mass index
CRP	C-reactive protein
GDM	gestational diabetes mellitus
HbA <sub>1c</sub>	glycated haemoglobin A <sub>1c</sub>
MIG	Metformin In Gestational diabetes

significant reduction in the incidence of neonatal jaundice and a lower incidence of admissions to the special care baby unit. However, it is important to note that some patients cannot tolerate metformin because of unpleasant gastrointestinal side effects and in this group of patients, insulin remains an option with its long standing record of safety in pregnancy.

It is important to remember that there is a linear relationship between the levels of pre-conception HbA<sub>1c</sub> and embryopathy. Data need to be explored using agreed definitions for an agreed lowest level of HbA<sub>1c</sub> where absolute risks, including hypoglycaemia, will be minimal to develop local protocols. The fluctuation of glucose and insulin levels during pregnancy make the concept of using a long-acting insulin analogue seem very attractive. However we must wait for results of properly designed controlled studies with appropriate long-term follow-up of the newborns and the mothers before implementing this approach.<sup>5</sup>

## Pre-conception management

In women with type 1 and type 2 diabetes it is important to focus on pre-conception advice to encourage tighter glycaemic

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control and regular intake of folic acid. Similar principles are applicable to obese women planning for a family as they are at increased risk of developing GDM. However, the exact impact of these interventions on the aberrant metabolic milieu of diabetic women remains elusive. While pre-conception advice has been shown to have a clinically significant effect, less than 50% of patients adhere to it.<sup>6</sup> It has been argued that a higher dose of folic acid would be beneficial. However, data from Canada suggest that the prevalence of vitamin B12 deficiency has increased since the introduction of mandatory folic acid fortification in 1997, with a concomitant tripling of neural tube defects attributable to B12 deficiency over the same period.<sup>7</sup> This begs important research questions of whether B12 deficiency contributes to poor outcomes in the type 1 diabetic mother and what should be the optimal dose of pre-conceptual folic acid. This is important as there is a linear relationship between the levels of pre-conception HbA<sub>1c</sub> and embryopathy.

### Challenges of obesity in the West Indies

We have a unique contribution from the West Indies in this issue.<sup>8,9</sup> Caribbean nations are populated by people drawn from West Africa, the Indian subcontinent and the Far East. So here humanity is at the crossroads of cultural integration. This population provides a unique environment to study the interplay of genes as some children of today in the Caribbean may have inherited genes from three or four different ethnicities. In the Caribbean, obesity is manifest in adults in their 20s and 30s and there is a concomitant high prevalence of diabetes and cardiovascular disease in women of reproductive age. In this population metformin is proving useful in the treatment of polycystic ovaries and GDM.<sup>8</sup>

Insulin resistance syndrome manifests itself in young adolescent females who present with gross obesity, menstrual disorders and hirsutism, which often fail to respond favourably to tried and tested medication. This scenario is described by Teelucksingh and Dan<sup>9</sup> who successfully managed their patient with bariatric surgery. This case also illustrates that there is a genuine need for establishing multidisciplinary clinics where endocrinologists, gynaecologists, laparoscopic surgeons with an interest in bariatric surgery, dieticians and psychologists are involved in the integrated management of these patients. These two papers clearly demonstrate that we need to learn from physicians and gynaecologists working in different parts of the world. By sharing these experiences, we will learn more in order to develop unified approaches to deal with these challenges, which are going to affect our clinical practice in future.

### Understanding placental development and pregnancy-induced insulin resistance

There has been a renewed interest in the relationship between placental function and adverse outcome of the newborn. The placenta is fascinating, being the interface between foetus and mother. The human placenta is a powerhouse and expresses all

known cytokines; and some of these adipokines are key players in the regulation of insulin action. It will be fascinating to study the possible interaction between the placenta and adipose tissue in understanding pregnancy-induced insulin resistance as this interplay becomes more evident in GDM.

Obesity and GDM are insulin-resistant states with diverse abnormalities in oxidative stress, protein glycation and cellular processes. These in turn lead to impaired endothelial function, vascular inflammation and haemostasis; processes which give rise to impaired function of the microcirculation causing abnormalities in placental function leading to foetal hypoxaemia. Doshani and Konje<sup>10</sup> in this edition, provide a fascinating account of the interplay of cytokines, leptin, resistin, and fibroblast growth factor 2 to enhance insulin resistance in the GDM mother. Similarly, the foetal environment is also changed in diabetes, and elevated levels of insulin, leptin and other cytokines have been reported. Interestingly, concentrations of leptin were more than two-fold higher and concentrations of IL-6 and CRP were also elevated in obese women compared with lean women. High CRP correlates with endothelial dysfunction and impaired insulin sensitivity. It can be postulated from these observations that there is a common pathway of biochemical aberrations that explains various morbidities associated with obesity and insulin resistance and are manifested at variable magnitudes among women with obesity, GDM and types 1 and 2 diabetes. HbA<sub>1c</sub> has a higher affinity for oxygenation and thus there is reduced oxygen delivery to the intervillous space and reduced utero-placental blood flow leading to foetal hypoxaemia. Hypoxia is a potent stimulator for angiogenesis.

Herein Evans<sup>11</sup> demonstrates that although the classic diabetic placenta is usually bulky and oedematous, often with a thick oedematous umbilical cord, it is the coiling index of umbilical cords which is significantly different in diabetic populations. GDM is associated with either hypercoiled or non-coiled cords, which are considered responsible for an increase in neonatal morbidity and mortality. She points out that it is the spiralling of the vessels which is thought to provide stability against buckling or compression. Such an effect is seen predominantly in placentas of type 1 diabetes. However, data in GDM appear variable. The challenge for the researchers is to investigate the effect of metformin on placental development and function to evaluate whether the benefits of using metformin are related to its vascular protective effect rather than its insulin sensitising effects in the face of insulin resistance. Metformin has been classified as a class B drug by the US Food and Drug Administration, as there remains an unanswered question about the potential foetal effects of this agent. Metformin crosses the placenta and is concentrated in the foetal compartment with umbilical artery and vein levels being up to twice those seen in the maternal serum. The concept of programming *in utero* for metabolic syndrome is widely accepted. Would metformin with its high concentration alter foetal programming to decrease the likely future development of the metabolic syndrome?<sup>12</sup>

## Obesity, male infertility and sexual functions

In our previous themed edition on obesity and reproduction (*Br J Diabetes Vasc Dis* January–February 2009), we explored the relationship of male obesity and its impact on fertility. It is worrying that obesity rates in adult men are rising exponentially year on year. A recent British survey<sup>13</sup> showed that 53% of the population was overweight or obese, yet in obese men only 67% recognised themselves to be overweight or obese. It has been reported that overweight and obese men have an up to 50% higher rate of sub-fertility compared with normal weight men. This effect persists even when confounding factors such as male age, smoking, alcohol use and female partner obesity have been controlled. Obesity is strongly linked to reduced spermatogenesis, poor quality of sperm and a reduced percentage of normal sperm morphology. Obese men have been shown to demonstrate a relative hyperoestrogenic hypogonadotropic hypogonadism with BMI being negatively correlated with testosterone and inhibin concentration and positively correlated with oestrogen levels. Furthermore higher levels of serum leptin have been associated with reduced androgen levels, possibly by direct regulation of testicular steroidogenesis. Kay and Barratt<sup>14</sup> in this issue observe that there are limited clinical data on the treatment of infertility in obese men. Furthermore there are no data to suggest that drastic weight reduction makes an immense change in the sperm parameters. Therefore researchers need to mount well designed prospective studies to assess the impact of weight loss in men on fertility outcomes. Furthermore in morbid obesity the role of bariatric surgery should be prospectively evaluated, especially its effect on sperm count.

The continuing infertility in men with type 2 diabetes is also related to erectile dysfunction, secondary to significantly lower levels of free testosterone. They suffer from lethargy, loss of libido, depressed mood and a markedly reduced frequency of intercourse.<sup>15</sup> A low testosterone level has also been shown to be an independent factor for increased cardiovascular risk. In this edition Hackett<sup>16</sup> reports that up to 46% of patients might be candidates for testosterone replacement treatment. Hackett *et al.*<sup>17</sup> also observed that in their population sample of 488 men with type 2 diabetes a markedly lower level of free testosterone was inversely associated with increased BMI, waist circumference and HbA<sub>1c</sub>. Their results clearly make a case for assessment of total and free testosterone estimation in routine diabetic care. Healthcare commissioners may wish to include this information in their future purchasing agreements. Our understanding of the pathophysiology of lower testosterone levels and its precise impact on multiple organs of humans who are obese but are not diabetic still needs more research.

Do exercise and adjuvant metformin treatment in obese males have a similar positive effect as observed in females? We will welcome contributions to this area.

## Conclusion

Overweight and obesity have far reaching effects on the individual and society and until we can curb our increasing adiposity we have to find better ways to manage the clinical sequelae.

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