Pragmatic use of metformin in pregnancy based on biopsychosocial model of health

Sir,

We have read with interest various articles on gestational diabetes mellitus (GDM), published in IJEM.[1-3] We observe controversy regarding not only screening, but also management of GDM. This is especially true regarding use of oral anti-diabetic agents (OAAs). The initial focus for achieving glycemic control uses life-style modifications. By altering diet and exercise, up to 90% of patients with GDM will achieve target blood glucose levels.[3] For several years, human insulin has been the only treatment option for diabetes that could not be controlled by diet and life-style modifications alone.[3] Insulin has proven efficacy and safety. Over the last 15 years, randomized controlled trials (RCTs) and meta-analysis of these RCTs comparing OAAs (metformin and glyburide) with insulin have shown equivalent safety and efficacy both for maternal and fetal health outcomes.[4] The results are still short-term, but safety data from RCT for off springs followed until 2 years of age is encouraging.[5] The long-term effects are still

unknown, resulting in cautious use of OAAs in pregnancy. This caution is justified with the current level of evidence.

The economic burden of GDM management is an issue which has not been addressed adequately. In resource challenged societies like India, the cost of treatment of GDM with insulin is many fold higher (10 fold in a study by Rai *et al.*) as compared with metformin.[6] Thus, OAAs may become through financial necessity, a preferred treatment in developing countries. This rationale is supported by the fact that use of insulin for GDM (which may comprise as few as 3-6 weeks of treatment), requires labor-intensive teaching and monitoring. Injection of insulin at multiple times in the day may be inconvenient. Hypoglycemia and weight gain are other feared risks. There is also the bitter truth of gender discrimination in health-care, observed in many communities across the world, especially in South Asia.[7] The diagnosis of GDM adds to stress at an individual as well as family level. While this burden is not avoidable, the added stress of having to take injectable therapy is perceived as social stigma by many women and families. Because of all these sempiternal factors, there is a need to objectively assess the possible role of OAAs, especially metformin, in GDM.

In view of similar efficacy of metformin (pregnancy category B drug) and insulin in women with GDM (RCTs based results), selected women with GDM may be candidates for OAAs. We propose a pragmatic, individualized approach to use of metformin in mild GDM [Table 1], based on the biopsychosocial model of health.[8] Mild GDM is defined as an abnormal result on an oral glucose-tolerance test but a fasting glucose level below 95 mg/dl.[9]

A multinational study in regions with high prevalence of GDM, including India, will provide valuable evidence and guidance in this regard. This will help in individualizing therapy appropriately, rather than generalizing results of trials to all populations. Hence, we feel that there is a need for a large RCT to compare metformin with insulin in GDM patients keeping biopsychosocial indications in mind. The evidence gathered from such a trial will provide answers to many questions and may help in taking care of the health-care burden, psychological stress and social stigma in future. Whether such a study, focusing on a cheap, non-patented, "non-profitable" molecule such as metformin, will find sponsors is an altogether different and yet unanswered, question!

Table 1: Pragmatic use of metformin in mild GDM[$], based on biopsychosocial health model

Domain	Clinical situations
Contraindications	
General	All contraindications to metformin use in non-pregnant individuals
Pregnancy specific	Ketonuria
	Any evidence of maternal distress
	Any evidence of fetal distress
Indications	
Biological	As monotherapy
	GDM not responding to medical nutrition therapy
	GDM detected during late third trimester
	Poor compliance with the treatment plan when the treatment plan includes insulin
	Lack of skills for self-management with insulin therapy and monitoring
	As combination therapy, with insulin
	Uncontrolled hyperglycemia, not responding to optimized insulin regimes
	Unwanted weight gain with insulin therapy
Psychological	If the suggestion of insulin causes extreme psychological stress
	When suggestion of insulin causes patient to reduce nutritional intake in order to maintain glycemia
Social	If the suggestion of insulin causes extreme family/social stress
	Financial burden
	In health-care settings where insulin is not available or accessible
	In health-care settings where regular glycemic monitoring is not feasible
Precautions	Regular fetal surveillance
	Regular maternal surveillance
	Obstetric monitoring
	Medical monitoring

[$]An abnormal result on an oral glucose-tolerance test but a fasting glucose level below 95 mg/dl (Ref.: Landon *et al.*). GDM: Gestational diabetes mellitus

Bharti Kalra, Yashdeep Gupta[1]

Department of Obstetrics and Gynaecology, Bharti Hospital, Karnal, Haryana, [1]Department of Medicine, Government Medical College and Hospital, Chandigarh, India

Corresponding Author: Dr. Bharti Kalra, Department of Obstetrics and Gynaecology, Bharti Hospital, Kunjpura Road, Karnal - 132 001, Haryana, India.
E-mail: brideknl@gmail.com

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