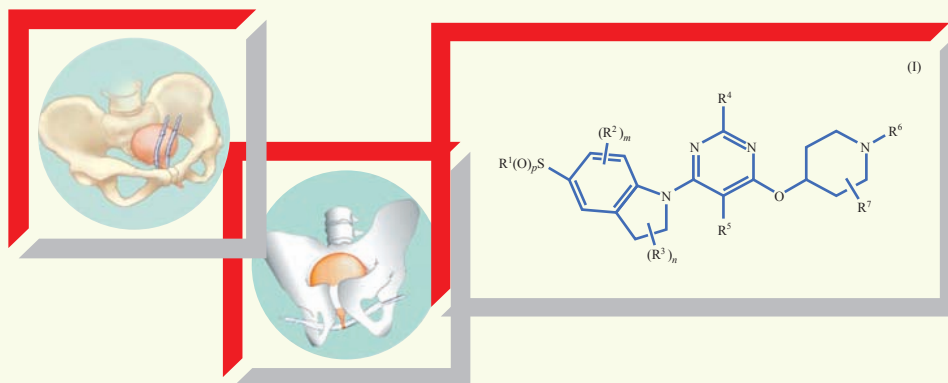


# WOMEN'S HEALTH

Volume : 7, No : 1 January - March 2014



**M**anagement of urinary incontinence in women: focus on Prevention

**O**ral Hypoglycemic agents in Pregnancy

#### Editorial Board

- **Dr. Omar Akramur Rab**  
MBBS, FCGP, FIAGP
- **Mohammad Hanif**  
M. Pharm, MBA
- **Imran Hassan**  
M. Pharm

#### Executive Editor

**Shanta Roy**  
M. Pharm  
e-mail: [shanta-roy@squaregroup.com](mailto:shanta-roy@squaregroup.com)

#### Editorial Note:

Dear Doctor,

It's our immense pleasure to publish the 1<sup>st</sup> issue of Women's Health Newsletter in this year. Like the previous issues, we have focused on some important health matters regarding Women. In this issue we are focusing on "Management of urinary incontinence in women" and "Oral Hypoglycemic agents in Pregnancy".

Your comments and suggestions will encourage us for upcoming issues. Please participate in quiz competition and win prizes.



**SQUARE**  
PHARMACEUTICALS LTD.  
BANGLADESH



## Management of urinary incontinence in women: focus on Prevention

### Introduction:

Female urinary incontinence is a common problem, which can have a significant impact on quality of life as well as social exclusion. Its precise incidence is not fully known, but is estimated to affect up to 35% of the total female population over the age of 60 years, with women twice as likely as men to experience incontinence. Though it is a common problem it remains vastly under-reported and under-treated. The three most common types of incontinence affecting women are Stress Urinary Incontinence (SUI), Urge

Urinary Incontinence (UUI), and Mixed Urinary Incontinence (MUI). It is important to correctly identify the type of incontinence from the symptoms described as the management of each type differs considerably. It is also important to have a clear understanding of the risk factors involved in the etiology of incontinence so that a holistic approach to management can be implemented. Many cases of mild incontinence will respond well to basic lifestyle changes and conservative management strategies and will not require onward referral to specialist services.

### Common types of incontinence and the International Continence Society (ICS) definitions

Type of incontinence	Definition
Stress Urinary Incontinence (SUI)	Involuntary loss of urine on effort or physical exertion or on sneezing or coughing
Urge Urinary Incontinence (UUI)	Involuntary loss of urine associated with urgency
Mixed Urinary Incontinence (MUI)	Involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing

### Risk factors for urinary incontinence in women

Intrinsic	Environmental	Obstetric and gynecological
Family history	Age	Pregnancy and childbirth
Race	Obesity	Pelvic surgery
Neurological conditions (multiple sclerosis, Parkinson's disease)	Raised intra-abdominal pressure (chronic cough, exercise)	Pelvic radiotherapy
Anatomical abnormalities (congenital abnormalities, pelvic organ)	Urinary tract infections Medication (diuretics, antidepressants) Food stuffs (caffeinated or carbonated drinks, alcohol)	

### Risk factors for developing Urinary Incontinence and the role of Prevention:

Urinary incontinence prevalence is a public health issue and there is a growing body of evidence-based research on primary prevention. The use of behavioral modification programs, including weight loss, Pelvic Floor Muscle Training (PFMT) and diet modification, has been investigated in at-risk populations, including older women, women of child-bearing age, obese women, those with diabetes, and in women who are physically active. Epidemiological studies have identified risk factors for urinary incontinence in women (alone and in combination). Many risk factors may be modified with changes in lifestyle, such as weight loss in overweight women. Obesity alone, and in combination with type 2 diabetes, is a well recognized independent risk factor for urinary incontinence in women. Age and the direct influence of estrogen continue to be controversial and intensely debated. Parity, pregnancy and childbirth, independent of labor and delivery, are primary risk factors.

### Behavioral modification for prevention of Urinary Incontinence:

Primary prevention of urinary incontinence using behavioral modification programs, including life-style changes (weight loss, diet modification), has been investigated in at-risk populations, including older women, women of childbearing age and obese women with diabetes. Varied methods of delivering behavioral modification have been shown to be successful in several different studies, would be cost effective and appeal to community-dwelling adults. A recent Cochrane review found that women who received regular supervision in a pelvic floor training program were more likely to report improvement than women doing Pelvic Floor Muscle Training (PFMT) with little or no supervision.

### Reduction of foods and fluids:

**Maintaining weight:** : Obesity is clearly an established and modifiable risk factor for urinary incontinence in women. Several systematic reviews demonstrate a positive association between

BMI more than or equal to 25 and SUI, but more recently, obesity has also been identified as a high risk factor for other lower urinary tract symptoms (LUTS) including urgency, frequency, Overactive Bladder (OAB) and UUI (Urge Urinary Incontinence). There is evidence that obesity increases intra-abdominal pressure, places stress and strain on the pelvic floor structures, leading to weakening of the pelvic floor muscles, nerves and blood vessels.

Reduction in urinary incontinence has been observed in morbidly obese women who have had dramatic weight loss after bariatric surgery and in women who achieved moderate loss through supervised weight-loss programs. Study showed that 6-month behavioral intervention targeting weight loss reduced the frequency of self-reported urinary incontinence episodes (mean weekly reduction of 47%) among overweight and obese women as compared with a control group (28%) and reduced UUI (Urge Urinary Incontinence) episodes by 42% (compared with 26% in the control group). Even moderate weight loss can improve LUTS in overweight women. In fact, loss of 5–10% of body weight, sustained over a 12-month period, can decrease incontinence episodes by as much as 70%. In a recent trial weight loss was recommended as an initial treatment for incontinence in overweight and obese women. Based on the current evidence, moderate weight reduction modifies the risk of urinary incontinence in women and if women maintain their weight within recommended guidelines, then urinary incontinence may be prevented.

### **Managing Diabetes:**

LUTS and changes in bladder function occur in over 50% women with diabetes. Diabetes may affect bladder nerve function as well as microvascular inflammatory processes, so efforts to improve diabetic control and prevent diabetes may serve to decrease the urinary incontinence risk. Urinary incontinence is the most common complication associated with type 2 diabetes in women. Diabetic neuropathy can lead to bladder sensory disturbances causing bladder over distension and large point-void residuals, resulting in further complications. The risk of pathological bladder changes and urinary incontinence may be reversed if diabetes can be prevented by lifestyle interventions including weight loss and physical activity. Weight loss appeared to be the driving force behind the reduced prevalence and incidence of urinary incontinence and SUI. They found that each 1 kg of weight loss was associated with a 3% reduction in the odds of developing urinary incontinence and SUI specifically. So modest weight loss of 5–10% reduced the odds of developing urinary incontinence ( $P= 0.01$ ). It has been recommended that weight loss intervention should be considered for prevention of urinary incontinence in overweight obese women with diabetes.

### **Role of physical activity and incontinence:**

About one out of three women leak urine during physical activity and exercise regardless of age, but the association between physical activity and incontinence remains complex. It is clear that high impact exercises, involving abrupt, repeated increases in intra-abdominal pressure, are a direct cause of incontinence.

Consequently, those women who experience urinary incontinence with physical activity may feel less able and willing to engage in such sports. A prevention strategy would be to incorporate PFMT into fitness and training programs when young girls start to participate in competitive sports and in adult women who exercise regularly, especially those athletes participating in high-impact sports.

### **Role of estrogen replacement in urinary incontinence:**

MUI with OAB symptoms of urgency and frequency are common in women 50 years or older, with menopause and concurrent estrogen deficiency currently being attributed to its occurrence. Numerous studies and reviews have examined the premise that estrogen levels may play an important role in preventing incontinence; however, new data have recently been reported that contradict this premise. Although there is some evidence to suggest that oral estrogens have been reported to increase maximum urethral pressure and lead to symptomatic improvement in 65–70% of women, recent publications do not confirm this or conclude that it is not useful as a treatment strategy for SUI. Although the evidence supporting the use of estrogen in lower urinary tract dysfunction remains controversial, there are considerable data to support its use in urogenital atrophy and the vaginal route of administration correlates with better symptom relief by improving vaginal dryness, pruritus and dyspareunia, and greater improvement in cytological findings, without raising serum estradiol levels. In addition, local vaginal estrogen administration has been shown to improve LUTS and reduce the incidence of recurrent urinary tract infections.

### **Pelvic floor muscle exercises in preventing urinary incontinence in childbearing women:**

Although urinary incontinence occurs in women who have never given birth, women who have had even one vaginal delivery are significantly more likely to report urinary incontinence than their nulliparous counterparts. Pregnancy alone leads to mechanical and hormonal changes with impaired pelvic floor muscle strength. Childbirth has the potential to damage the sphincter complex, muscles, and nerves of the pelvic floor that control urine flow and defects occur more frequently in women who deliver large babies, and have undergone forceps or vacuum extraction delivery, anal sphincter laceration and episiotomy. Cesarean delivery may reduce the risk of pelvic floor trauma, but it is not entirely protective. Maternal obesity also appears to be a high risk factor for the development of urinary incontinence during pregnancy and after delivery and weight-loss postpartum may play a role in preventing urinary incontinence. PFMT is recommended during pregnancy and after delivery, both for prevention and treatment of incontinence. Level 1 and 2 evidence indicates that intensive antenatal PFMT, which includes one to one instruction, checking for correct muscle contraction, and continued supervision of training can prevent the development of urinary incontinence during pregnancy (35–36 weeks' gestation) and short-term (6 weeks–6 months) postpartum in primiparous women. PFMT is effective in preventing and reversing some pregnancy-related urinary incontinence for up to 6 months after delivery.

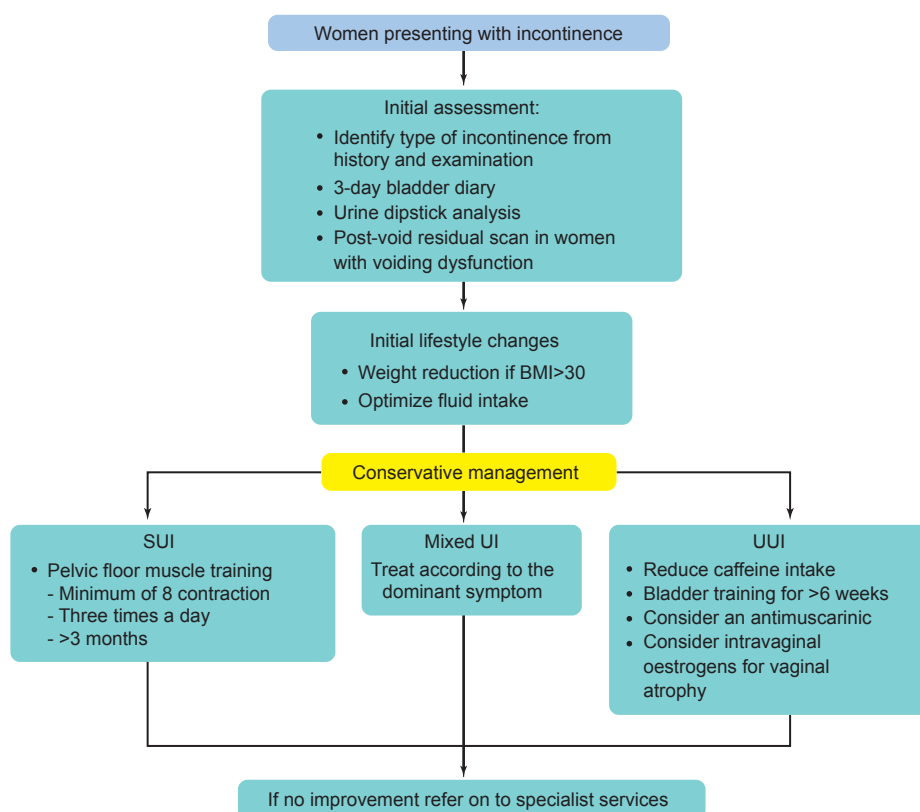
## Pharmacological Management of Urinary Incontinence:

If bladder training fails, then it is acceptable to consider a trial of an antimuscarinic in patients with no contraindications to their use, before referral on to specialist services. The NICE guidelines recommend the initial use of nonproprietary oxybutynin, followed by newer generation antimuscarinics such as solifenacin, tolterodine, or trospium. If vaginal atrophy is clearly evident on vaginal examination, a short course of intravaginal estrogen (once daily for 2 weeks, then once or twice weekly for 2 months) can often improve symptoms of urgency and help in the management of UUI. Duloxetine has been shown in prospective, randomized studies to both decrease frequency of incontinent episodes and increase quality of life in patients with SUI. These effects are typically small and the chance for cure are remote.

## Conclusion:

The initial assessment and treatment of women with urinary incontinence can be readily accomplished in the community when following a clear diagnostic algorithm. Appropriate referral on to

specialist urological services is required when conservative measures fail or when preliminary tests raise “red flag” results. When being referred for specialist review, patients should be aware that further assessment may involve more invasive tests, such as urodynamics and cystoscopy. Depending on the severity of the incontinence and the underlying cause, surgical management options for the treatment of SUI include midurethral tapes, fascial slings, colposuspension, periurethral bulking agents, and artificial urinary sphincter placement. Options for the treatment of UUI include intravesical botulinum toxin injections or sacro neuromodulation. All these procedures carry a greater risk to the patient, making it imperative that all conservative options available have been fully explored. Like diabetes and obesity, urinary incontinence is a chronic problem that requires a preventive strategy. Behavioral modifications that include lifestyle changes and pelvic floor muscle exercises have the potential to prevent urinary incontinence, but may need to be adopted early in life by those individuals who are obese and/or have diabetes and are in risk.



An algorithm for the initial assessment and treatment of female urinary incontinence

## Oral Hypoglycemic agents in Pregnancy

### Introduction:

Diabetes is one of the common medical disorders complicating pregnancy and its incidence in women of reproductive age group is increasing globally. Gestational diabetes constitutes 88 %, and Type 2 diabetes accounts for eight percent of all cases of diabetes in pregnancy. The overall incidence of gestational diabetes is 3–6 % with a variation of 2–15 % observed, depending on the diagnostic criteria used. The concerns of diabetes are mainly related to its maternal and fetal complications. Although a significant reduction in perinatal mortality has been observed in the last decade, there is little change in the perinatal morbidity. The HAPO Study Cooperative Research Group demonstrated strongly that the adverse perinatal outcomes were related to hyperglycemia in pregnancy resulting in fetal hyperinsulinemia, macrosomia and birth trauma. Achieving euglycemia optimizes the outcome in diabetic pregnancies as recommended by the American College of Obstetricians and Gynecologists and American Diabetes Association thereby promoting maternal wellbeing and reducing the adverse perinatal outcomes.

The initial treatment in these patients with Type 2 diabetes and gestational diabetes is by diet modification and in the event of failure of control with diet, the treatment is shifted to insulin to achieve tight glucose control with no risk of placental transfer. However, insulin therapy can be inconvenient because of the needs for multiple injections, its associated cost, pain at the injection site, need for refrigeration, and skillful handling of the syringes. This has led to the exploration of oral hypoglycemic agents as an alternative to insulin therapy.

### Pharmacodynamics of Oral Hypoglycemic Agents:

The use of oral hypoglycemic agents in patients with hyperglycemia in pregnancy has been one of the biggest controversies in the treatment of diabetes and pregnancy. A variety of oral hypoglycemic agents is now available for lowering blood glucose. For patients with pregnancy and hyperglycemia, the most important is that the agent should not cross the placenta from the maternal to fetal circulation in significant amounts.

### Sulfonylurea:

Sulfonylureas have been in use since decades in the management of Type 2 diabetes and are insulin secretagogues. They act by stimulating the release of insulin from the functional cell mass of pancreas binding to specific receptors in pancreatic beta cell plasma membrane resulting in closure of adenosine triphosphate channels. This initiates the opening of the calcium channels and leads to increase in cytoplasmic calcium thereby stimulating insulin release. They have been identified to enhance insulin sensitivity in peripheral tissues. The pathogenesis of both gestational diabetes and Type 2 diabetes are insulin resistance and inadequate insulin secretion, and hence the beneficial role of sulfonylurea is evident.

The first generation sulfonylureas are acetohexamide, chlorpropamide, tolazamide, and tolbutamide. Specifically, there are concerns regarding chlorpropamide like inducing neonatal hypoglycemia, and retrospective case control studies identified threefold increase in congenital anomalies in babies of Type 2 diabetes patients exposed to these drugs during the organogenesis period, and hence they are not recommended in pregnancy.

The second generation of sulphonylurea like glyburide does not cross the placenta in significant amounts. Studies showed that there were no detectable glyburide levels in the umbilical cord despite the achievement of therapeutic concentrations of the drug in the maternal blood. Glyburide's inability to cross the placenta, despite its low molecular weight, is attributed to its high protein-binding capacity of 99.8 %. However, another possible explanation proposed that there was pumping back of the glyburide load back into the maternal system by an unidentified placental transport system. Glyburide reduced the fasting blood glucose (FBG) levels by 2–4 mmol/L (36–72 mg/dL) as well as glycosylated hemoglobin HbA1c by 1–2 %. The absence of fetal adverse effects such as malformations and hypoglycemia makes it an acceptable treatment option.

### Biguanides:

Metformin is the second generation biguanide that acts by increasing the insulin sensitivity and thus reducing the insulin resistance. It reduces the rate of hepatic glucose production, hepatic glycogenolysis, and increases the insulin-stimulated uptake of glucose in skeletal muscles. The biguanides does not stimulate the fetal pancreatic cells to produce insulin and hence are not associated with neonatal hyperinsulinemia. The peak plasma half-life is 2–5 h. The mechanism of clearance of metformin is by renal tubular secretion with minimal protein binding. This reflects the need for dose adjustment in pregnancy because of the increased glomerular filtration in pregnancy. Studies have identified that metformin crossed the placenta but had minimal effect on transplacental flux. The transfer in human can be used safely in lactation.

### Thiazolidinedione:

Thiazolidinediones act on the peroxisome proliferator-activated receptor reducing the insulin resistance. The pharmacodynamics of these drugs are similar to glyburide. Despite the similarities to biguanides, these drugs cross the placenta as demonstrated in rats resulting in delayed growth and insulin resistance. A study done by Scientist Chan et al. with rosiglitazone given to pregnant women undergoing surgical termination of pregnancy between 8 and 12 weeks of pregnancy, and rosiglitazone was detected in 19 out of 31 (61 %) fetal samples. One study suggested that troglitazone (the first thiazolidinedione agent) reduced the incidence of new onset diabetes in patients with gestational diabetes. However, troglitazone

**Table 1 Classification of oral hypoglycemic drug**

Sulfonylureas	<b>First generation</b> <ul style="list-style-type: none"> <li>• Acetohexamide</li> <li>• Chlorpropamide</li> <li>• Tolazamide</li> <li>• Tolbutamide</li> </ul> <b>Second generation</b> <ul style="list-style-type: none"> <li>• Glyburide/ glibenclamide</li> <li>• Glipizide</li> <li>• Glimepiride</li> </ul>
Biguanides	<ul style="list-style-type: none"> <li>• Metformin</li> </ul>
Thiazolidinediones	<ul style="list-style-type: none"> <li>• Pioglitazone</li> <li>• Rosiglitazone</li> </ul>
Meglitinides	<ul style="list-style-type: none"> <li>• Repaglinide</li> <li>• Nateglinide</li> </ul>
Alpha-glucosidase inhibitors	<ul style="list-style-type: none"> <li>• Acarbose</li> <li>• Miglitol</li> </ul>

was withdrawn because of its hepatotoxicity. The second generation thiazolidinedione (rosiglitazone and pioglitazone) was more potent, not hepatotoxic and was effective in reducing the decline of beta cell function in patients with type 2 diabetes. One case study in a woman with polycystic ovarian syndrome on rosiglitazone at the time of conception was reported where rosiglitazone was subsequently discontinued and pregnancy was uneventful.

#### Meglitinides:

Meglitinides are insulin secretagogues like sulfonylurea. Their actions were similar to sulfonylurea but via different receptor. There is no data regarding the use of nateglinide during pregnancy. Until further data is available, it is prudent not to use this drug in pregnancy. A randomized controlled trial with repaglinide and insulin demonstrated that the pre and postprandial glucose levels were the same in the treatment and the control groups and there was no difference in the fetal and neonatal outcome.

#### Alpha Glucosidase Inhibitors:

Acarbose acts by slowing the absorption of carbohydrates from the intestines thereby reducing the postprandial hyperglycemia. As acarbose acts at the gastrointestinal tract, there is no blood stream transfer to the placenta. It is less effective than glyburide in reducing the glycemic levels and hence its use is restricted in combinations with glyburide or metformin.

#### Clinical Practices of Oral Hypoglycemic Agents in Pregnancy:

Baris Akincia *et al.* investigated the practice patterns of clinicians (family physicians, internists, and obstetricians) in Turkey with respect to diabetes in pregnancy. The results suggest that there is considerable variation in the clinical practice patterns. Internists were more likely to use insulin analogs. A significant number of physicians stated that they used oral hypoglycemic agents, and a considerable number of family physicians have used the drugs which have not been proven to be safe in pregnancy. Hence, the conclusion was made that there was room for improvement in the

knowledge and practices related to the use of oral hypoglycemic agents in pregnancy.

#### Current Developments:

After the discovery of insulin, attempts were made to create oral insulin. The success of oral insulin depends on its ability to resist the enzymatic degradation, during its transit in the gastrointestinal system. The advances in this area have resulted in understanding the techniques of effectively delivering oral insulin and the development of oral insulin. Several systems that provide protection to insulin during the transit in the gastrointestinal system have been developed. These systems include matrices that use medium chain fatty acids designed to release insulin in the duodenum, a hepatic-directed vesicle (HDV) containing liposomes encapsulating insulin, which delivers it directly into the liver cells; an absorption enhancer; and solubilizer that enhances the drug absorption in the small intestine; and low molecular weight chemical entities that act as carriers for the drug. ORMD-0801 is an oral insulin that has completed its phase I trials, and the results are encouraging as it has proven to be safe, well tolerated, and insures consistent reduction in glucose and C-peptide. The other alternative routes of insulin delivery being developed are buccal and inhaled, whereby insulin is delivered directly into the mouth via a metered dose spray (Rapid Mist device).

#### Treating pregnant woman with oral hypoglycemic:

Currently both glyburide and metformin are classified by as Category B drugs for use in pregnancy. Glyburide does not cross placenta and has strong evidence of its efficacy which is well established in the large randomized trial by Langer *et al.* This conclusion by Langer *et al.* regarding glyburide is upheld in various randomized controlled trial and observational studies. However, one needs to keep in mind that glyburide still fails in about 20 % of women. The other oral hypoglycemic agent demonstrated to be effective is metformin especially in polycystic ovarian syndrome where it is beneficial in reducing the pregnancy loss, reducing the development of gestational diabetes, and improving the insulin sensitivity. The benefits of using metformin in pregnancy is well demonstrated in the randomized controlled trial by Scientist Rowen *et al.* 2008 with metformin in gestational diabetes trial (MiG trial). It is also concluded that metformin is not associated with increased perinatal complications as compared with insulin, and that the women preferred metformin to insulin treatment. The follow up of these exposed children of age 2 years studied in the MiG-TOFU trial reveals that metformin exposed infants had more subcutaneous fat and less visceral fat, which may probably result in increased insulin sensitivity pattern of growth in future. Acarbose appears promising because of its pharmacodynamic profile in the absence of systemic effects. Although this drug has also been categorized as FDA category B drug, there is a need for further randomized trials comparing acarbose with other oral hypoglycemic agents and insulin before validating its effectiveness. Further studies are mandatory to recommend the use of thiazolidinediones and meglitinides in pregnancy.

## The controversies of treatment:

Even if the patient with hyperglycemia in pregnancy does not have high abnormal glucose intolerance, all experts agree that treatment either by lifestyle modification only, or lifestyle modification plus pharmacologic treatment is always needed to reach the excellent target goals. For years insulin was the only treatment of choice for this patient. The choice of insulin is still controversy, especially the used of insulin analogue. This kind of insulin used in pregnant diabetic patients just started 10 years ago. The human insulin is preferable since it has been used for years without side effect in the neonates or even long-term effect among the children.

The use of oral agents, metformin and glibenclamide, is still the biggest controversy in diabetology. American Diabetes Association in the recent Clinical Practice Recommendation 2012, the diagnosis of women with hyperglycemia follow the new criteria but there was no statement about the treatment, which means that insulin is still the only pharmacologic therapy. In 2009 the International Diabetes Federation of World Health Organization statement as follow "for women with GDM who exceed predetermined glycemic goals, insulin is the preferred treatment. Where insulin cannot be afforded, or where circumstances make its use hazardous, then oral agents can be the only option". In many places, insulin is still the only choice for the treatment of diabetic patients complicated with hyperglycemia.

## Conclusions:

The overall evidence suggests that oral hypoglycemic agents are safe alternative in the presence of mild-to-moderate hyperglycemia. They can be an effective alternative in developing countries where resources and availability of the insulin is of concern. As the incidences of type 2 diabetes and gestational diabetes increase, it becomes important to have alternatives to women who are not adequately controlled with diet and exercise and are unable to be compliant with standard insulin therapy. The advantages of oral hypoglycemic agents are simple to administer, convenient, pain free, and cost effective. The current evidence from the data as discussed in this review supports the use of glyburide and metformin in the management of Type 2 diabetes and gestational diabetes. There is still a room for improvement in the knowledge and practices of prescribing these agents among the health providers. The providers should communicate to the women that there are no data available on the long-term health of the offspring's exposure to glyburide or metformin, as the safety aspects of these oral hypoglycemic drugs are limited to the prenatal period. We therefore need more randomized control trials to provide more information on the long-term follow up on neonatal function and cognitive development.

Ref: Kavitha N, De S, Kanagasabai S. Oral Hypoglycemic Agents in pregnancy: An Update. The Journal of Obstetrics and Gynecology of India. 2013; 1-6.

## Congratulations!

*The Winners of* **WOMEN'S HEALTH** *Quiz Competition* Vol-6 No-3, October - December 2013

**Dr. Shekh Samsun Nahar Sammi**  
MBBS, MCPS, FCPS (Paed)  
Medilab Health Centre, Station Road  
Kishoreganj

**Dr. Saleha Alam**  
MBBS, FCPS-1, Registrar (Gynae & Obs.)  
DMCH, Dhaka

**Dr. Hasanat Jahan**  
MBBS, MCPS, DGO, Consultant (Gynae)  
General Hospital, Pabna

**Dr. Nilufa Musharrat Afza Begum**  
MBBS, MCPS (Obs & Gyane)  
Diploma in MCH & FP, Consultant (Obs & Gyane), CWCH  
Ashulia, Dhaka

# Calbo<sup>®</sup> Forte

Calcium+Vitamin C+Vitamin D



## Adds Sparkle to Calcium, Vitamin C & D

Calbo<sup>®</sup> Forte is required in

- ☀ Calcium, Vitamin C and Vitamin D deficient condition
- ☀ Pregnancy & lactation
- ☀ Periods of rapid growth (childhood, adolescence) & old age
- ☀ Osteoporosis



# Calbo<sup>®</sup> C

Calcium + Vitamin C



## For healthy Bone & Teeth

- ☀ Utilizes state-of-the-art technology to deliver Calcium with Vitamin C
- ☀ Fulfills demand of the cells of the body, including those of the heart, nerves and muscles
- ☀ Helps to maintain normal blood cholesterol level
- ☀ Maintains healthy immune system



Since 1958



**SQUARE**  
PHARMACEUTICALS LTD.  
BANGLADESH

[www.squarepharma.com.bd](http://www.squarepharma.com.bd)

[facebook.com/SquarePharmaLtd](https://www.facebook.com/SquarePharmaLtd)

[twitter.com/SquarePharmaBD](https://twitter.com/SquarePharmaBD)

