VOLUME - 10, ISSUE - 08, AUGUST- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Surgery

GLYBURIDE VERSUS METFORMIN : NEONATAL COMPLICATIONS IN THE PHARMACOLOGICAL MANAGEMENT OF PATIENTS WITH GESTATIONAL DIABETES. SYSTEMATIC REVIEW OF THE LITERATURE.

Alexander Garcia Castañeda*	Physician and Surgeon, Universidad Industrial de Santander. *Corresponding Author
Maria Camila Ruiz	Physician and Surgeon, Universidad Industrial de Santander.
Carolina Garcia	Physician and Surgeon, Universidad Industrial de Santander.
Lida Marcela Vega Mesa	Physician, Universidad de Santander. Bucaramanga, Santander, Colombia
Gennifer Andrea Gomez Toloza	Physician, Universidad de Santander. Bucaramanga, Santander, Colombia
Duvan Alexander Betancourt	Physician and Surgeon Universidad de Antioquia. Medellin, Antioquia, Colombia.

KEYWORDS : Gestational Diabetes, Glyburide, Glybenclamide , Metformin, Pregnancy Complications, Perinatal Death, Congenital Abnormalities.

INTRODUCTION

Diabetes mellitus can be defined as a group of metabolic disorders characterized by high blood glucose concentrations (1) . In general, type I diabetes is frequently associated with a deficiency secondary to the destruction of insulin-producing β cells (2) . Meanwhile, type II diabetes is the result of a progressive increase in insulin resistance with a relative deficit of it (3) . On the other hand, gestational diabetes is defined by The American Diabetes Association (ADA) as one that is diagnosed in the second or third trimester that is not clearly type 1 or type 2 diabetes (4) .

The frequency of presentation of gestational diabetes differs around the world. It is estimated that the highest prevalence of this disease is found in the Middle East and North Africa reaching 12.9%, followed by Southeast Asia and the Western Pacific with 11.7%, South and Central America with 11, 2% and North America with 8.9%, with the European continent standing out as the lowest with 5.8% (5) . Given the frequency of this pathology, numerous studies have been carried out on it and the evidence in various publications showing a direct relationship between gestational diabetes and adverse maternal-fetal outcomes has been clear. The Hyperglycaemia and Adverse Pregnancy Outcome Study (HAPO), conducted in 23,316 women, found that blood glucose values with a standard deviation above the normal range are significantly associated with birth weight above the 90th percentile, neonatal hypoglycemia, hyperbilirubinemia , dystocia of shoulders, premature delivery, pre-eclampsia and need for cesarean section (6) . Additionally, fetal malformations, polyhydramnios , prolonged gestations, instrumented delivery, heart disease, respiratory distress, fetal and maternal trauma have been described (7) .

Insulin has traditionally been considered the treatment of choice for the management of gestational diabetes when metabolic control cannot be achieved with diet and exercise (8). Insulin is known for its great ability to lower serum glucose values in the short, medium and long term; which implies a great impact on the control of diabetes mellitus (8). However, insulin has two characteristics that hinder its pharmacological adherence in a large volume of patients. In the first instance, its route of administration is subcutaneous, which generates fear and anxiety in patients (9) . Additionally, the mode of employment and general care measures require adequate training, which in our environment is not always possible. (10).

Some oral drugs such as Metformin and Glyburide have been proposed in the management of the disease. Different studies show a similar efficacy profile of these with respect to insulin in the control of glycemic values (11) , they are easily accepted by patients, their dosage is simpler and they may have a lower cost (6) . However, adverse neonatal effects have been demonstrated including macrosomia , neonatal hypoglycemia, and congenital malformations (12) (13) (14) . For this reason, the Food and Drug Administration (FDA) has not endorsed the administration in pregnant women due to the lack of knowledge abouttheir safety profile, given the divergence in the results of the available studies, the small number of publications in this regard. , insufficient population size and methodological errors.

Taking into account the prevalence of the disease, the efficacy of the treatment and the greater adherence to oral treatment; It is essential to clarify the potential risk that the prenatal administration of these oral hypoglycemic agents may pose to fetal health. Additionally, distinguishing the safety profile between Metformin and Glyburide allows differentiating its usefulness in pregnant women and thus determining the best therapeutic option for this particular population. Therefore, this systematic review aims to describe and compare neonatal complications in mothers who received Metformin versus treatment with Glyburide .

MATERIALS AND METHODS

Search Strategy

To identify the studies included in this review, a systematic literature search was carried out, using the approach recommended by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyzes) (15) in the MEDLINE database (16) .

The articles included do not have an established time universe, with language limitation to articles in Spanish, English, Portuguese and French. The search was carried out during the month of November of the year 2016, with the last consultation carried out on November 30 of the same year.

The search algorithm combined 7 MeSH terms that fully represented the population of interest and the problem posed: 1. Gestational Diabetes, 2. Glyburide, 3. Glybenclamide , 4. Metformin, 5. Pregnancy Complications, 6. Perinatal Death, 7 Congenital Abnormalities.

Selection Of Studies

The data were extracted independently by a pair of team members, firstly by title - the two reviewers selected articles based on the title from the database according to their criteria and in a second step another pair of reviewers analyzed that inclusion [2] evaluating this selection again - and later by abstract through the same system. In case of disagreement, the judgment was made through open discussion.

Subsequently, the full text of the articles obtained by these filters was read, choosing those that met a series of inclusion criteria such as: randomized clinical trial (RCT) type studies, meta-analysis, systematic reviews, studies of cases and controls, related to neonatal complications of children of mothers with gestational diabetes treated with Metformin or Glyburide , as well as those studies that have the association measures (relative risk, Odds ratio) and their confidence intervals or with the necessary data for calculating them, such as the number of exposed and unexposed population. As exclusion criteria studies where thedrugs of interest are compared with other pharmacological interventions and not with each other, those systematic reviews that evaluated studies already included in the search, studies where the sample presents other comorbidities (hypertensive disorders associated with pregnancy, liver disorders, maternal and perinatal infection) and population with multiple pregnancy.

Finally, for the evaluation of the selected articles, individual qualitative assessment scales were used (STROBE (17) for case-control studies, CONSORT (18) for ECAC and PRISMA (15) for meta-analysis). For the synthesis and analysis of the results, the pooled Odds Ratios (OR) with 95% confidence intervals (CI) were taken into account , as well as the Relative Risk (RR) of the included studies. For those studies that did not have the association measures evaluated, the MEDCALC application (virtual version) was used to calculate the ORs and RRs based on their exposed and unexposed populations. The identification, manipulation and control of bibliographic references and files was carried out with the Mendeley program (version 1.10.1).

RESULTS

The search in the database using the algorithm found a total of 67 articles as shown in the flow diagram in Figure 1. At first, a paired selection was made by titles, where 42 articles were selected, a second filter by reading the abstract eliminating 12 articles, a third selection was carried out by the complete reading of the articles, excluding 9 articles because they did not have association measures or the necessary data to calculate them, 6 articles because they did not study neonatal complications, 4 systematic reviews because they only evaluated articles already included in the study, 2 articles because they evaluated associations with other drugs and 1 because it was another type of study. A total of 8 articles were selected for the systematic review, of which 6 were classified as high quality, 1 as moderate quality and 1 as low quality. The detailed results of the quality evaluation of the 8 articles are presented in the figure 1.

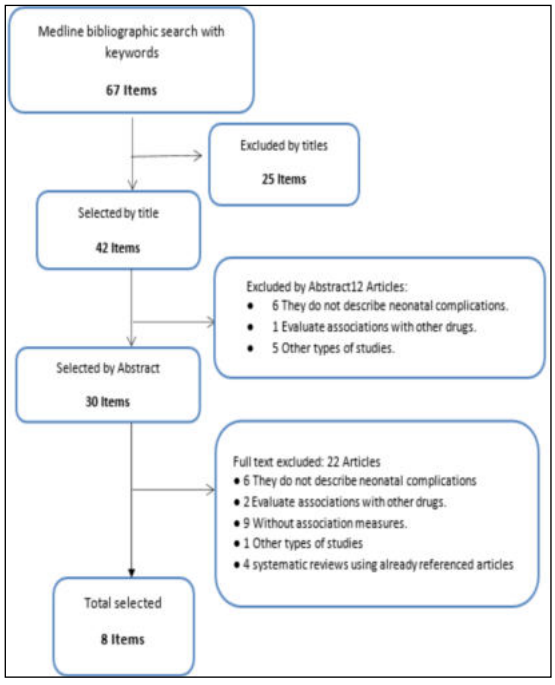

Figure 1. Flow diagram.

A total of 39,190 women with gestational diabetes were studied in the included articles, of which 3 are systematic reviews with meta-analysis, 3 randomized controlled clinical trials, 1 meta-analysis, and 1 case-control study. The characteristics of the included studies are described in Table 1.

Table 1. Characteristics of the 8 articles included in the systematic review.

AUTHOR - YEAR	COUNTRY	STUDY TYPE	INTERVENTION	DOSE	POBLACIÓN EVALUADA	Measure of Association (95% CI)			
						MACROSOMY	HYPOGLYCEMIA	SMALL GESTATIONAL AGE	CESÁREAN
			Metformina vs Gliburida						
Balsells, et (2015) (19)	Barcelona	Systematic review and meta-analysis	Gliburida vs Insulina	--	Metformina vs Gliburida: 349	RR 0.33 (0.13-0.81)	RR 0.86 (0.42-1.77)	RR 1.23 (0.28- 5.36)	RR 1.99 (0.32-12.4)
			Metformina vs Insulina						
	Estados	Systematic			Total: 2509				
Carroll, et	Unidos	review and	Metformina vs			RR 0,33	--	RR 0,44	--
al.(2015)		meta-	Gliburida	--		(0,13- 0,81)		(0,21 a 0,92).	
(20)		analysis							
			Gliburida vs Metformina		Total: 2800				

Jiang et al.(2015) (21)	China	Meta-analysis	Metformina vs Insulina	--	Gliburida vs Metformina: 334	OR 3,17 (0,84-12,00)	OR 1,09 (0,56-2,15)	--	OR 0,72 (0,28-1,90)
			Gliburida vs Insulina						
				G: 2,5 mg, máx 15 mg.					
George et al. (2015) (22)	India	Controlled clinical trial	Gliburida vs Metformina	M: 500 mg, máx 2500 mg.	Total: 159 M: 79 G: 80	RR 0.74 (0.17-3.2)	RR 20.7 (1.20 a 348.03)	--	--
		Retrospective							
Michael H. Shannon (2016) (23)	EEUU	obser vational case-control study	Gliburida vs Metformina	--	Total: 32.635 M: 2591	OR 1,53 (1,38-1,691)	--	--	--
					G: 4992				
Muhammad Amin (2015) (24)	Tailandia	Systematic review and meta-analysis	Gliburida vs Metformina	--	Total 508	RR 1,94 (1,03-3,66)	RR 1,92 (0,31-12,02)	--	RR 0,86 (0,55-1,34)
Moore et al. (2010) (25)	Estados Unidos	Controlled clinical trial	Gliburida Vs Metformina	G: 2,5 mg dos veces al día, máx 20 mg/día. M: 500 mg/días, máx 2 g/día..	Total: 149 M: 75 G: 74	RR 4.0 (0.464-35.42)	RR 0.33 (0.01 - 8.16)	--	--
Silva J et al. (2010) (26)	Brasil	Controlled clinical trial	Gliburida vs Metformina	G: 2,5 mg, máx 20 mg. M: 500 mg, máx 2500 mg.	Total: 81 M 32 G 40	RR 2.40 (0.52-11.09)	RR 0.93 (0.35 - 2.50)	--	RR 1.02 (0.75-1.39)

Author	Year	Type of study	Scale	Hit Items / Total Items	Quality
Patterson, et	2015	Systematic review and meta-analysis	PRISMA	21/27	High
Carroll, et al.	2015	Systematic review and meta-analysis	PRISMA	11/27	Low
Jiang et al.	2015	Meta-anayisis	PRISMA	24/27	High
George et al.	2015	Controlled clinical trial	Consort	35/37	High
Michael H. Shannon	2015	Retrospective observational case-control study	Strobe	23/28	High
Muhammad Amin	2015	Systematic review and meta-analysis	PRISMA	25/27	High
Moore et al.	2010	Controlled clinical trial	Consort	20/25	High
Silva J et al.	2010	Controlled clinical trial	Consort	19/25	Moderate

Complications Related To Fetal Weight

The relative risk of presenting macrosomia when comparing glyburide versus metformin was evaluated in 4 of the 8 articles, of which 2 found an increased risk in patients who took glyburide compared to those who took metformin , this risk ranged between 2.40- 4.05 , but in none was it statistically significant. However, in the article by Muhammad Amin et al they found significantly statistical values (RR 1.94; 95% CI: 1.03-3.66), however it isnecessary to take into account that this outcome combined large newborns for gestational age and macrosomia in a single outcome. In the article by George et al, the use of glyburide was a protective factor to present macrosomia compared to metformin RR 0.74, however it was not statistically significant (95% CI 0.1713 to 3.2030).

The odds ratio for presenting macrosomia when comparing glyburide versus metformin was evaluated in 2 of the 8 articles, in the one by Jiang et al it showed an increase in the possibility of presenting macrosomia in the group that took glyburide compared to metformin with OR 3.17 However, it was not statistically significant (95% CI 0.84-12.00). The Michael H. Shannon study showed an increase in the possibility of presenting macrosomia in the group that used glyburide compared to metformin with OR 1.15 and it was not statistically significant either (95% CI 0.98-1.346)

The relative risk of presenting macrosomia when comparing metformin versus glyburide was evaluated in 2 of the 8 articles, these were that of Balcells et al, and that of Carroll et al, who evaluated the same clinical trials in their meta-analyzes for this outcome. that the RR measurement coincided

being 0.33 with a 95% CI of (0.13 to 0.81), according to this, the use of metformin is a protective factor for macrosomia compared to glyburide, being statistically significant.

Regarding infants small for gestational age, they were evaluated in 2 articles, Balcells et al. with a RR of 1.23, 95% CI (0.28- 5.36) and Carroll, et al. with a RR of 0.44, 95% CI (0.21-0.92), the latter being the only one with a statistically significant result, which indicates that Metformin would be a protective factor for small for gestational age compared to the Gliburida .

The study by Moore et al. was the only one who evaluated the association of shoulder dystocia. The glyburide was a risk factor for shoulder dystocia 3.04, with no significant statistical value (95% CI 0.12 - 73.44).

Complications Of Neonatal Adaptation

The relative risk of presenting Apgar <7 at the first minute of life in neonates, whose mothers were treated with Glyburide compared to Metformin according to the Silva et al study, was a risk factor of 1.60; however, they did not find statistically significant values (95% CI 0.15-16.86). On the other hand, the systematic review and meta-analysis by Balcells et al, found that the relative risk of Apgar <7 at the first minute of life in neonates whose mothers were treated with metformin was 0.46 compared to glyburide, but it was not significant either (95 % IC 0.04-5.0). The study by Moore et al. evaluated the incidence of Apgar <7 at the first minute of life, but there were no cases in both groups. Additionally, two studies evaluated Apgar at five minutes, Silva et al found that newborns of mothers with gestational diabetes who were treated with glyburide had a relative risk of 0.27 compared to those who were treated with Metformin and Patterson et al, found that indiabetic mothers managed with metformin it was 2.77, without being statistically significant in either of the two studies.

A recent randomized controlled clinical trial (George et al) also found that neonates born to mothers with gestational diabetes who were managed with glyburide compared to Metformin had respiratory distress syndrome (RDS) as a complication , with glyburide being a risk factor of 1.97 , however without significant statistical value (95% CI 0.37 - 10.47).

Metabolic Complications

The results in 7 of the 8 articles show treatment with Glyburide versus Metformin as a risk factor for hypoglycemia with RR values ranging between 1.09 -20.7, this is opposite to the result presented by Moore et al and Silva et al, where the glyburide a protective factor RR of 0.33 (95% CI 0.014) and 0.93 (95% CI 0.35 to 2.5) respectively. However, none of the above presents values with statistical significance.

On the other hand, Balcells et al found that the use of Metformin is a protective factor for the same result with a RR 0.86, despite this it does not constitute a statistically significant finding (95% CI 0.42-1.77). Regarding hyperbilirubinemia, George et al, found that newborns whose mother received glyburide treatment present a risk factor for the need for phototherapy but without statistical significance , RR 1.96 (95% CI 0.6-2.37).

Other Neonatal Complications

Prematurity as a complication was evaluated in 4 of the included articles, in which the relative risk in the children of pregnant women treated with Glyburide compared to Metformin varied between 0.65 - 1.15, these values being statistically non-significant. On the other hand Silva et al, and Muhammad Amin et al, found Glyburide management as a protective factor (0.80 95% CI : 0.24-1.779) and (0.80 95% CI; 0.05-12.29) respectively, but without being statistically significant. The meta-analysis carried out by Jiang et al, also found Glyburide as a protective factor to present prematurity compared to Metformin with an OR of 8.56 95% CI (0.43-169.70) but like the other studies these values are not statistically significant.

Balcells et al, was the only article included that evaluated perinatal death and stillbirth, where the exposure group was the patients treated with Metformin compared with Glyburide, finding that they are protective factors with a RR of 0.92, 95% CI (0.06 -11.6) and 0.92, 95% CI (0.06-14.6) respectively, however these results are not considered statistically significant.

Newborns treated with Glyburide compared to Metformin who required admission to the neonatal intensive care unit were evaluated in 4 articles with statistically non-significant results with a RR between 0.25 - 1.52.The association of caesarean section with the use of oral hypoglycemic agents (Metformin or Glyburide) during pregnancy was evaluated in 4 of the 8 studies. Three studies coincide in the use of Metformin during pregnancy as a risk factor for requiring high- flow delivery, while the study by Silva et al found that the use of Gl iburide is a risk factor of 1.02 (95% CI 0.75- 1.39) compared to the use of metformin during pregnancy. None of the studies were statistically significant.

DISCUSSION

The results found in this study remain controversial regarding the management of patients with gestational diabetes. In the literature, only one article found a statistically significant association in relation to neonates weighing more than 4000 grams, with glyburide being a risk factor when jointly evaluating macrosomic and large-for-gestational age neonates , when compared with Metformin (21) ; a finding that was not evidenced by taking macrosomia as an outcome in isolation.The other statistically significant finding was in relation to neonates small for gestational age, where it was found that Metformin would be a protective factor to present this complication compared to Glyburide (20).

In total, 13 neonatal complications were evaluated, including changes in neonatal weight, difficulty in adaptation, metabolic disorders, among others. However, 11 were not statistically significant. This is probably due to the fact that the population volumes were not representative especially in the randomized clinical trials. Taking into account that the object of study was pregnant women, it is possible to infer that the main limitation in obtaining a number of individuals to study is the ethical implication of the maternal-fetal binomial (27) (28) . Similarly, it is considered necessary to recognize that despite not being statistically significant for the aforementioned, Glyburide compared to Metformin was a risk factor for presenting adverse events in neonates in most studies.

It remains to be analyzed whether the macrosomia evaluated as an isolated variable is a statistically significant complication, or if this association is given by the evaluation in conjunction with the large variable for gestational age.

Given the divergent findings regarding adverse neonatal outcomes, it is not possible to recommend a specific oral hypoglycemic agent for treatment in women diagnosed with gestational diabetes until new evidence is available to confirm or rule out the findings presented here.

Strengths And Limitations

The development of the study had some limitations due to the lack of experience on the part of the work group, which delayed the synthesis of the results, however, as a strength of

the study, it is important to highlight that the searches carried out were effective since they included all of the articles that evaluate the variables of interest carried out in thispopulation because the same articles found in this search were included in all the studies reviewed, likewise, the articles included have a satisfactory checklist that guarantees their high quality, so our study condenses the most up-to-date evidence about neonatal complications in children of pregnant women treated with Metformin or Glyburide .

CONCLUSION

In this systematic review, it was identified that there is a deficiency in the number of clinical trials that compare Glyburide versus Metformin to assess adverse neonatal outcomes, which could be validated because when analyzing the different meta-analyzes they always used the same clinical trials, in addition to such trials the population was small; Therefore, it is necessary to carry out clinical trials that include a larger population, in order to define whether the oral hypoglycemic agents used in pregnancy (Metformin or Glyburide) have sufficient safety for the health of the neonate and thus be able to use them as alternative treatment. in gestational diabetes because it is already known that the efficacy of these drugs is similar to insulin, which is the ideal drug approved for use in gestational diabetes when metabolic control does not work (8) (29).

REFERENCES

1. Ruiz C, Arribas B, Arribas L. Chronic diseases and pregnancy (III): diabetes mellitus and obesity. AMF. 2016; 12 (7): 407–11.
2. Epidemiology, presentation, and diagnosis of type 1 diabetes mellitus in children and adolescents - UpToDate [Internet]. [cited 2016 Dec 16]. Available at: https://ezproxy.uis.edu.co:2729/contents/epidemiology-presentation-and-diagnosis-of-type- 1-diabetes-mellitus-in-children-and-adolescents?source=search_result&search=diabetes % 20mellitus% 20type% 201 & selectedTitle = 1 ~ 150
3. Association AD. STANDARDS OF MEDICAL CARE Standards of Medical Care in Diabetes - 2016. J Clin Appl Res Educ. 2016; 39 (January).
4. Association AD. Classification and diagnosis of diabetes. Diabetes Care. 2016; 39 (January): S13–22.
5. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Curr Diab Rep. 2016; 16 (1): 7.
6. Group THSCR. Hyperglycemia and Adverse Pregnancy Outcomes. N Engl J Med. 2008; 358 (19): 1893–902.
7. Álvarez E, Domínguez P, Alves M, Domínguez J, González A. Biochemical risk factors for diabetes mellitus in women with previous gestational diabetes. Ginecol Obstet Mex. 2016; 84 (7): 428–39.
8. NICE guideline. Diabetes in pregnancy: management from preconception to the postnatalperiod.2008;Availablea t : https://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of- diabetes-and-its-complications-from-preconception-to-the-postnatal-period -51038446021
9. Nicholson W, Baptiste-Roberts K. Oral hypoglycaemic agents during pregnancy: The evidence for effectiveness and safety. Best Pract Res Clin Obstet Gynaecol. 2011; 25 (1): 51–63.
10. Lenz R, Ramírez J, Gac R, Lorca E. Difficulties in the rational prescription of insulin: The perception of doctors treating diabetic patients in primary health care. Rev Med Chil. 2010; 138 (3): 281–8.
11. Marcela Buitrago-Leal, Saulo Molina-Giraldo. Safety and effectiveness of oral hypoglycemic agents in women with gestational diabetes. Review of the bibliography. Ginecol Obstet Mex. 2014; 82: 454–64.
12. Renda E, Faraci M, Di Prima FAF, Valenti O, Hyseni E, Monte S, et al. Treatment of gestational diabetes: oral hypoglycemic agents or insulin? J Prenat Med. 2011; 5 (3): 63–4.
13. Valdés Rubio E, Soto-Chacón E, Lahsen M. R, Barrera H. C, Candia PP Efficacy of oral hypoglycemic agents in the metabolic control of patients with gestational diabetes mellitus. Rev Med Chil. 2008; 136 (7): 915–20.
14. Amin MR, Hossain MZ, Miah MT, Yasmin R, Chowdhury MFI, Hoque MA. Are Oral Hypoglycemic Agents Contraindicated in Pregnancy! J Bangladesh Coll Physicians Surg. 2010; 28 (2): 8-10.
15. Urrútia G, Bonfill X. PRISMA statement: a proposal to improve the publication of systematic reviews and meta-analyzes. Med Clin (Barc). 2010; 135 (11): 507–11.
16. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. National Center for Biotechnology Information [Internet]. [cited 2016 Dec 16]. Available at: https://www.ncbi.nlm.nih.gov/
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Guidelines for communication of observational studies. Gac Sanit. 2008; 22 (2): 144: 150.
18. Cobos-Carbó A, Augustovski F. CONSORT 2010 statement: checklist update for reporting parallel group randomized clinical trials. Med Clin (Barc). 2011; 137 (5): 213–5.
19. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ. 2015; 350 (2): h102.
20. Carroll D, Kelley KW. In women with gestational diabetes requiring drug treatment, glibenclamide may be inferior to insulin and metformin: metformin (plus insulin when required) performs better than insulin. Evid Based Med. 2015; 20 (4): 127.
21. Jiang YF, Chen XY, Ding T, Wang XF, Zhu ZN, Su SW. Comparative efficacy and safety of OADs in management of GDM: network meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2015; 100 (5): 2071–80.
22. George A, Mathews JE, Sam D, Beck M, Benjamin SJ, Abraham A, et al. Comparison of neonatal outcomes in women with gestational diabetes with moderate hyperglycaemia on metformin or glibenclamide - A randomized controlled trial. Aust NZJ Obstet Gynaecol. 2015; 55 (1): 47–52.
23. Shannon MH, Wintfeld N, Liang M, Jovanovic L. Pregnancy snapshot: A retrospective, observational case-control study to evaluate potential effects of maternal diabetes treatment during pregnancy on macrosomia. Curr Med Res Opin. 2016; 1–37.
24. Amin M, Suksomboon N, Poolsup N, Malik O. Comparison of Glyburide with Metformin in Treating Gestational Diabetes Mellitus: A Systematic Review and Meta- Analysis. Clin Drug Investig. 2015; 35 (6): 343–51.
25. Moore LE, Clokey D, Rappaport V, Curet L. Metformin Compared With Glyburide in. Obstet Gynecol. 2010; 115 (1): 55–9.
26. Silva JC, Pacheco C, Bizato J, De Souza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. Int J Gynecol Obstet. 2010; 111 (1): 37–40.
27. INTERNATIONAL ETHICAL GUIDELINES [Internet]. [cited 2016 Dec 16]. Availableat: http://www.cioms.ch/publications/guidelines/ pautas_eticas_internacionales.htm
28. THE MINISTER OF HEALTH. RESOLUTION N or 008 430 1993; By which the scientific, technical and administrative standards for health research are established. [Internet].1993.Availableat:https://www.unisabana.edu.co/fileadmin/Documentos/Investigacion/comite_de_etica/Res 8430_1993__Salud.pdf
29. Gestational diabetes mellitus: clinical management guidelines for obstetricians – gynecologists. CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN – GYNECOLOGISTS. 2013; 122: 406–16.