First-trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis

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TABLE OF CONTENTS
• Introduction
• Methods
• Results
  Studies evaluating pregnant women with type 2 diabetes
  Studies evaluating pregnant women affected by PCOS
  PCOS studies excluded from the meta-analysis but reporting relevant data on birth defects
• Discussion

BACKGROUND: Metformin is generally considered a non-teratogenic drug; however, only a few studies specifically designed to assess the rate of congenital anomalies after metformin use have been published in the literature. The objects of the present study were to review all of the prospective and retrospective studies reporting on women treated with metformin at least during the first trimester of their pregnancy and to estimate the overall rate of major birth defects.

METHODS: Databases were searched for English language articles until December 2013. Inclusion criteria for the meta-analysis were: a case group of women with PCOS or pre-pregnancy type 2 diabetes and first-trimester exposure to metformin; a disease-matched control group which was not exposed to metformin or other oral anti-diabetic agents; and a list of the major anomalies in both the study and the control groups. A random effects model was used for the meta-analysis of data, using odds ratios. Studies not fulfilling the inclusion criteria for the meta-analysis but reporting relevant data on major malformations in women diagnosed with PCOS were then used to estimate the overall birth defects rate.

RESULTS: Meta-analysis of nine controlled studies with women affected by PCOS detected that the rate of major birth defects in the metformin-exposed group was not statistically increased compared with the disease-matched control group and that there was no significant heterogeneity among the studies. The metformin-exposed sample was composed of 351 pregnancies and the OR of major birth defects was 0.86 (95% confidence interval: 0.18–4.08; P_heterogeneity = 0.71). By evaluating all of the non-overlapping PCOS studies reported in the literature, even those without an appropriate control group, the overall rate of major anomalies was 0.6% in the sample of 517 women who discontinued the therapy upon conception or confirmation of pregnancy and 0.5% in the sample of 634 women who were treated with metformin throughout the first trimester of their pregnancy. Regarding type 2 diabetic women, we did not identify a sufficient number of studies with metformin exposure during the first trimester to proceed with the meta-analysis.

CONCLUSIONS: There is currently no evidence that metformin is associated with an increased risk of major birth defects in women affected by PCOS and treated during the first trimester. However larger ad hoc studies are warranted in order to definitely confirm the safety and efficacy of this drug in pregnancy.

Key words: metformin / pregnancy / malformations / PCOS / type 2 diabetes
Introduction

Metformin is a widely used oral hypoglycemic agent which has been approved by the US Food and Drug Administration for the treatment of type 2 diabetes mellitus. Nevertheless, metformin is also commonly used to treat or prevent complications related to gestational diabetes mellitus and polycystic ovary syndrome (PCOS) (Velazquez et al., 1994; Diamanti-Kandarakis et al., 2010; Dhulkota et al., 2010; Gu et al., 2013).

Its mechanism of action lies in reducing the hepatic glucose production and the intestinal glucose absorption and increasing insulin sensitivity (Fig. 1). Since it does not increase the insulin production, the risk of hypoglycemia is minimized (Palomba et al., 2009b). Metformin is a weak base, a highly polar positively charged hydrophilic compound, with a low molecular weight and low binding capacity to plasma proteins; the elimination half-life ranges from 2 to 6 h, but it increases after repeated doses (~20 h) (Tucker et al., 1981; Bailey and Turner, 1996; Sambol et al., 1996; Scheen, 1996; Graham et al., 2011).

Metformin is usually well tolerated but transient mild gastrointestinal adverse effects (including diarrhea, nausea, vomiting, abdominal pain, flatulence) are common, especially during initiation of the therapy (Domecq et al., 2013; Vecchio et al., 2014). Other side effects reported are mild erythema in hypersensitive individuals and cobalamin deficiency. Lactic acidosis, a serious and often fatal complication, is rare and it primarily occurs in diabetic patients with significant renal insufficiency (Domecq et al., 2013; Vecchio et al., 2014).

Several studies have demonstrated that metformin freely passes through the placenta at term, exposing the fetus to therapeutic concentrations (Vanky et al., 2005; Charles et al., 2006; Nanovskaya et al., 2006; Kovo et al., 2008a; Eyal et al., 2010; Hemauer et al., 2010; Tertti et al., 2010; de Oliveira Baraldi et al., 2011). However there are no data about the placental transfer during the first trimester of pregnancy. Studies on animals are limited but do not suggest a major teratogenic effect of metformin (Tuchmann-Duplessis and Mercier-Parot, 1961; Denno and Sadler, 1994). In humans, several studies have been performed to evaluate the effects of metformin therapy before and during pregnancy; however only a few of these were specifically designed to estimate the rate of major birth defects in the offspring of metformin-exposed women.

A limited number of studies regarding the treatment of diabetic type 2 pregnant women with metformin during the first trimester are available, as women are usually switched to insulin as soon as they become pregnant in order to obtain a better control of the disease and reduce the risk of adverse outcomes associated with hyperglycemia (including fetal and neonatal death, congenital malformations, macrosomia, preterm delivery and pre-eclampsia) (Mathiesen et al., 2011). On the other hand, more trials evaluating the efficacy and safety of metformin during the second and third trimesters in the management of gestational diabetes have been performed; in most cases metformin was compared with insulin. Several reports and meta-analyses suggest that metformin is as effective as insulin in controlling gestational diabetes and preventing fetal, maternal and neonatal complications, especially in the case of mild gestational diabetes (Moore et al., 2007; Tertti et al., 2008, 2013; Balani et al., 2009; Dhulkota et al., 2010; Goh et al., 2011; Ijas et al., 2011; Gandhi et al., 2012; Niromanesh et al., 2012; Corbould et al., 2013; Gu et al., 2013; Hickman et al., 2013; Lautatzis et al., 2013; Mesdaghi et al., 2013; Spaulonci et al., 2013; Waheed et al., 2013); however the heterogeneity of studies, their often small sample size and the differences between treatment groups do not allow for firm conclusions to be reached.

Most of the studies with metformin exposure at conception and during the first trimester of pregnancy have involved women affected by PCOS and treated with metformin alone or in association with other drugs in order to induce ovulation.

Polycystic ovary syndrome is a common endocrinopath characterized by irregular or absent ovulation, hyperandrogenism and obesity. It has been estimated to affect ~5–10% of women in reproductive age (Polson et al., 1988; Carmina and Lobo, 1999). According to the Rotterdam consensus statement, the diagnosis of PCOS is made if two of the following criteria are present: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound, and if other etiologies are excluded (Rotterdam ESHRE/ ASRM-Sponsored PCOS Consensus Workshop Group, 2004a, b). Insulin resistance is thought to play a significant role in the pathogenesis (Diamanti-Kandarakis, 2008) and it is reported in ~65–70% of women diagnosed with PCOS (Chang et al., 1983; Dunaif, 1997; DeUgarte et al., 2005). Therefore metformin has been tested for the treatment of affected women before or during the ovulation induction with clomiphene. While there is evidence that clomiphene is associated with increased ovulation and pregnancy rates (Brown et al., 2005; Teede et al., 2011; Misso et al., 2012), there are still conflicting results regarding the role of metformin and clomiphene in the treatment of infertility in women affected by PCOS (Palomba et al., 2005b; Moll et al., 2007; Creanga et al., 2008; Tang et al., 2010; Misso et al., 2012). Moreover, recent meta-analyses of trials evaluating the efficacy of metformin in infertile women with PCOS suggest that metformin may improve the clinical pregnancy rate but does not increase the live birth rate (Siebert et al., 2012; Tang et al., 2012; Misso et al., 2013; Sun et al., 2013).

The majority of these studies were designed to evaluate the rates of ovulation, pregnancy and spontaneous abortions; moreover, when the follow-up continued until delivery, the live birth rate was reported without any information regarding the detection of birth defects. In several studies women were exposed to metformin only in the first weeks of pregnancy, as the treatment was suspended when there was a positive pregnancy test or evidence of the gestational sac on ultrasound. Moreover, even if the original sample size was sufficiently large, the actual number of women who ovulated and became pregnant was relatively small for the detection of birth defects.

To better define the teratogenicity of metformin, we have performed a systematic review and meta-analysis of controlled prospective and retrospective studies evaluating women treated with metformin during the first trimester of pregnancy.
Methods

A review of the literature was undertaken searching in PubMed MEDLINE and Web of Knowledge for English language articles, using, in combination with ‘metformin’, the key words ‘pregnancy’, ‘malformations’, ‘birth defects’ and ‘congenital abnormalities’. The last search was performed on 23 December 2013.

Inclusion and exclusion criteria are shown in Table I. The search strategy was limited to English language articles without any limits regarding the year of publication.

Both retrospective and prospective studies were included. Observational studies and case series were excluded. Studies without sufficient details regarding metformin exposure during pregnancy and birth defects in the offspring and studies evaluating exclusively the outcome of women with gestational diabetes after therapy with metformin during the second and third trimesters were also excluded. Bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analyses were evaluated for identification of additional studies.

The rate of major birth defects was calculated using all live births as a denominator (with multiple pregnancies being considered as singleton ones); terminations of pregnancies and spontaneous prenatal embryo-fetal losses were added only when major malformations were reported.

Major congenital anomalies were defined as structural abnormalities of medical, surgical or cosmetic relevance. All of the cases with abnormalities reported in the selected studies were included in the meta-analysis only after being reviewed and approved by all of the authors. Ongoing pregnancies and subjects with chromosomal anomalies and genetic diseases were also excluded in the calculation of birth defect rates.

After the initial database search, abstracts were evaluated independently by two reviewers (Cassina and Dona) for exclusion of reviews, meta-analyses and non-relevant studies, and the remaining studies were selected for careful review. Finally, relevant studies for the meta-analysis were reviewed by three authors (Cassina, Dona and Clementi).

Information on general details (title, authors, country, year of publication), participants (inclusion/exclusion criteria) and results (pregnancy outcomes and major congenital anomalies) were registered in ad hoc tables.

The meta-analysis was conducted using Review Manager 5.1 (Nordic Cochrane Centre). The heterogeneity was evaluated statistically by the Chi-squared test. A random effects model was used for the meta-analysis and the odds ratio (OR) for major birth defects was calculated. Results were displayed in tables and graphically by Forest plots.

Studies not fulfilling the inclusion criteria for the meta-analysis but reporting relevant data on major malformations in women with PCOS were used to estimate the overall birth defects rate which was compared with that of the general population.

Results

The selection process of the articles fulfilling the inclusion criteria for the meta-analysis is shown in Fig. 2. The search strategy we used resulted in 926 records in PubMed and 619 records in Web of Knowledge. After exclusion of reviews, meta-analyses and non-relevant studies, all of the remaining articles were carefully reviewed with particular attention to the methods and the results sections. In case of papers with overlapping recruitment periods and conducted by the same authors, only the most recent ones fulfilling the inclusion criteria were selected for the meta-analysis.

There were 15 non-overlapping studies reviewed by three authors; among these, 6 evaluated type 2 diabetic women and 9 evaluated PCOS-affected women treated with metformin during the first trimester of pregnancy.

Studies evaluating pregnant women with type 2 diabetes

There were six studies reporting information on the birth defect rate in type 2 diabetic women exposed during the first trimester of pregnancy to metformin selected for careful review; however only three of them completely fulfilled the inclusion criteria (Piacquadio et al., 1991; Helmuth et al., 2000; Rai et al., 2009), having an excessively small total sample size to draw firm conclusions and perform a meta-analysis. The characteristics of the six studies selected are presented in Table II.

Coetzee and Jackson (1984) performed a retrospective study during a 5-year period in order to analyze the pregnancy outcome in 171 women with established non-insulin-dependent diabetes: 78 were exposed to one or more hypoglycemic agents, including metformin (1750–2550 mg daily), during the first trimester. One birth defect (polydactyly) was observed in 20 patients prenatally exposed to metformin and glibenclamide during the first trimester and six malformations were reported in 89 patients exposed to insulin or untreated during the same period.

Piacquadio et al. (1991) analyzed the pregnancy outcome of 20 women with non-insulin-dependent diabetes with exposure to oral hypoglycemic agents during the first trimester between 1985 and 1990; drugs were discontinued at the first prenatal visit. The results were compared with those of 40 disease-matched women treated with insulin. Only one case was exposed to metformin and no malformations were observed at delivery. In the control group, among 36 live births, there were 6 cases with congenital anomalies (1 with bilateral T10 vertebral, 1 with ventricular septal defect and bilateral inguinal hernias, 1 with

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design: Retrospective or prospective study</td>
<td>Study design: Review, meta-analysis, case series, letters to the editor and animal studies</td>
</tr>
<tr>
<td>Population: Women of any age, ethnicity, BMI, with PCOS or pre-pregnancy type 2 diabetes</td>
<td>Population: No details on the period of exposure</td>
</tr>
<tr>
<td>Metformin exposure at least during the first trimester of their pregnancy</td>
<td>Comparison: No control group</td>
</tr>
<tr>
<td>Disease-matched control group</td>
<td>Healthy control group</td>
</tr>
<tr>
<td>No exposure to metformin or other oral anti-diabetic agents</td>
<td>Outcomes: Major birth defects rates</td>
</tr>
<tr>
<td>List of the major anomalies observed in both the exposed and the control group</td>
<td>Language: English</td>
</tr>
</tbody>
</table>
mild hypospadias, 2 with enlarged left cerebral ventricle, 1 with multiple malformations and CMV infection). The authors attribute this unexpected high incidence of malformations in the control group to unrecognized diabetes before pregnancy and late start in antenatal care.

Hellmuth et al. (2000) did not observe any major malformations among the infants of seven women who conceived while taking metformin, while one case of a balanced transposition of great vessels among seven cases with diet-treated pre-gestational type 2 diabetes (control group) was reported.

Hughes and Rowan (2006) performed a review of all pregnancies in women with Type 2 Diabetes between 1998 and 2003 at the National Women's Hospital in Auckland, New Zealand. There were 93 pregnancies exposed to metformin and the remaining 121 (control group) received other kinds of treatment (including other oral hypoglycemic agents). The authors report that the rate of major congenital anomalies (7.5%) among the infants of 85 type 2 diabetic women who had been treated with metformin during the first trimester of pregnancy was not different from the rate observed in the control group (10.7%). There are no data regarding the congenital anomalies observed, with the exception of one case of tetralogy of Fallot in the metformin-exposed group.

Another retrospective study (Ekpebegh et al., 2007) observed that the fetal anomaly rate in pregnancies of women treated with metformin and/or glibenclamide during the first trimester of pregnancy was so small that no meaningful analysis could be undertaken. However the number of infants prenatally exposed to metformin in the first trimester and the number and type of malformations are not reported. No fetal anomalies were observed in the control group which included type 2 diabetic women treated with diet or insulin.

Rai et al. (2009) reported on 60 pregnant women with type 2 or gestational diabetes who were prospectively followed-up; 30 women were treated with metformin (1500–2000 mg/day) and the remaining 30 women, recruited in a different obstetric unit, were treated with insulin. Among eight pre-pregnancy type 2 diabetic women, two were exposed to metformin during the first trimester and six were exposed to insulin. Only one major heart defect requiring surgery was observed in the insulin group.

**Studies evaluating pregnant women affected by PCOS**

The characteristics of the nine studies included in the meta-analysis are presented in Table III. In six out of the nine studies, the metformin therapy was discontinued upon confirmation of pregnancy. Overall there were 3 cases of major birth defects among 351 pregnancies in the metformin-exposed group and 2 cases among 178 pregnancies in the control group. Three cases with genetic diseases were excluded from the meta-analysis (one achondrodysplasia, one Kartagener’s syndrome and one Prader–Willi syndrome).

Glueck et al. (2001) performed a pilot study in order to evaluate whether metformin therapy would safely reduce the rate of first-trimester spontaneous abortion without teratogenicity; the authors prospectively enrolled 22 women with PCOS from the mid-western USA.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Period of study</th>
<th>Study design</th>
<th>Metformin exposure</th>
<th>Outcome in metformin-exposed group</th>
<th>Outcome in control-group</th>
<th>Malformations in metformin-exposed group</th>
<th>Malformations in control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coetzee and Jackson (1984)</td>
<td>South Africa</td>
<td>Not reported</td>
<td>R</td>
<td>1750–2550 mg/day during 1st trimester</td>
<td>20 births; 4 perinatal deaths</td>
<td>89 Births; 4 perinatal deaths</td>
<td>I polydactyly</td>
<td>6 unspecified malformations</td>
</tr>
<tr>
<td>Piacquadio et al. (1991)</td>
<td>USA (California)</td>
<td>1985–1990</td>
<td>R</td>
<td>During the first 7 weeks of gestation</td>
<td>1 LB</td>
<td>36 LB</td>
<td>None</td>
<td>I bifid T10 vertebra, I ventricular septal defect and bilateral inguinal hernias, 1 mild hypospadias, 2 enlarged left cerebral ventricle, 1 multiple malformations with CMV infection</td>
</tr>
<tr>
<td>Ekpebegh et al. (2007)</td>
<td>South Africa</td>
<td>1991–2000</td>
<td>R</td>
<td>1700 mg/day maximum</td>
<td>Not specified for 1st trimester exposureb</td>
<td>1 perinatal death among 30 births</td>
<td>Not specified, but the rate is reported to be small for 1st trimester exposure</td>
<td>None</td>
</tr>
<tr>
<td>Rai et al. (2009)</td>
<td>India</td>
<td>September 2004–August 2006</td>
<td>P</td>
<td>1500–2000 mg/day</td>
<td>2 births</td>
<td>6 births</td>
<td>None</td>
<td>I heart defect requiring surgery</td>
</tr>
</tbody>
</table>

R, retrospective; P, prospective; LB, live birth.

*aControls exposed also to other hypoglycemic agents.

*bIncludes pregnancies exposed to metformin and/or glibenclamide.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Period of study</th>
<th>Study design</th>
<th>Metformin exposure</th>
<th>Outcome in metformin-exposed group</th>
<th>Outcome in control group</th>
<th>Birth defects in metformin-exposed group</th>
<th>Birth defects in control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glueck et al. (2001)</td>
<td>USA (Ohio)</td>
<td>Not reported</td>
<td>P/R</td>
<td>1500–2550 mg/day throughout pregnancy</td>
<td>6 LB (+3 ongoing pregnancies); 1 LOSS (1st trimester)</td>
<td>6 LB; 16 LOSS (1st trimester)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Vandermolen et al. (2001)</td>
<td>USA (Virginia – Missouri)</td>
<td>Not reported</td>
<td>P</td>
<td>1500 mg/day until confirmation of pregnancy</td>
<td>4 LB; 2 LOSS</td>
<td>1 LB; 0 LOSS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Palomba et al. (2005b)</td>
<td>Italy</td>
<td>April 2003–September 2003</td>
<td>P</td>
<td>1700 mg/day until confirmation of pregnancy</td>
<td>28 LB; 3 LOSS (1st trimester)</td>
<td>10 LB; 6 LOSS (1st trimester)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Moll et al. (2006)</td>
<td>The Netherlands</td>
<td>June 2001–May 2004</td>
<td>P</td>
<td>500–2000 mg/day until confirmation of pregnancy</td>
<td>29 LB (+14 ongoing pregnancies); 14 LOSS (1 triplet pregnancy at 17 + 5)</td>
<td>41 LB (1 twin pregnancy) (+11 ongoing pregnancies); 13 LOSS (1 anencephalic fetus at 18 + 0)</td>
<td>1 anal atresia (1 Kartagener’s syndrome + hypospadias: excluded)</td>
<td>1 anencephaly</td>
</tr>
<tr>
<td>Nawaz et al. (2008)</td>
<td>Pakistan</td>
<td>January 2005–December 2006</td>
<td>P</td>
<td>1500 mg/day (Group A: until 4–16 weeks; Group B and C: until 32 weeks or over)</td>
<td>Group A: 32 LB; 8 LOSS Group B and C: 63 LB; 2 LOSS</td>
<td>26 LB; 6 LOSS</td>
<td>Group A: 1 polydactyly Group B and C: None</td>
<td>None</td>
</tr>
<tr>
<td>Johnson et al. (2010)</td>
<td>New Zealand</td>
<td>August 2003–February 2007</td>
<td>P</td>
<td>500–1500 mg/day until confirmation of pregnancy</td>
<td>30 LB (2 twin pregnancies); 9 LOSS (1 ectopic pregnancy)</td>
<td>15 LB (2 twin pregnancies); 3 LOSS (1 ectopic pregnancy), 1 TOP</td>
<td>None</td>
<td>1 hypoplastic heart (TOP)</td>
</tr>
<tr>
<td>Begum et al. (2013)</td>
<td>Bangladesh</td>
<td>December 2004–August 2009</td>
<td>P</td>
<td>1500 mg/day until confirmation of pregnancy</td>
<td>29 LB (1 twin pregnancy); 8 LOSS (4 spontaneous abortions; 3 blighted ovum, 1 ectopic pregnancy)</td>
<td>12 LB; 4 LOSS (3 spontaneous abortions; 1 blighted ovum)</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

R, retrospective; P, prospective; LB, live birth; LOSS, 1st–2nd trimester losses; TOP, termination of pregnancy.

*Previous pregnancies, not exposed to metformin, are used as controls.

*Only cases with previous pregnancies (not exposed to metformin) have been included; also three pregnant women who stopped therapy at 4–6 weeks of gestation have not been included due to the lack of data regarding birth defects in the previous pregnancies.
who conceived while receiving metformin, 1500–2550 mg/day. Among women who used metformin throughout pregnancy, 10 had 22 previous pregnancies without taking the drug and the authors compared the outcomes of the metformin-exposed pregnancies with those of the previous ones. There were six live births without major birth defects and one first-trimester spontaneous abortion among metformin-exposed pregnancies. In addition there were other three pregnancies we did not include in the meta-analysis because they were still ongoing, even if the ultrasound showed normal fetal development without congenital defects. Among the 22 previous pregnancies, there were 6 normal live births and 16 first-trimester spontaneous abortions. The authors also reported three pregnant PCOS-affected women who stopped therapy when pregnancy was first detected (4–6 weeks of gestation); however we could not include these cases in the meta-analysis because there are no data regarding the presence of birth defects in their previous pregnancies. There are several other studies performed by Glueck and collaborators, evaluating the pregnancy outcome of women exposed to metformin during the first trimester of pregnancy, but we could not include them in the meta-analysis because they did not fulfill all the inclusion criteria: in most cases only the live birth rate without comments on the presence or not of congenital anomalies was reported (Velasquez et al., 1994; Glueck et al., 2002a, b, 2004a, b, c, d, 2008, 2013).

Vandermolen et al. (2001) conducted a randomized double-blind, placebo-controlled trial evaluating the ovulation and pregnancy rates of anovulatory women diagnosed with PCOS and resistant to clomiphene. Twelve participants were treated with metformin (until a positive pregnancy test) while 15 participants received placebo. In the metformin group there were six pregnancies: two of these resulted in a spontaneous abortion and the other four in healthy infants delivered at term; in the placebo group there was only one pregnancy resulting in the delivery of a healthy infant at term.

Jakubowicz et al. (2002) conducted a retrospective study of all women with PCOS who were seen in the Endocrinology Clinic of the Hospital de Clinicas Caracas between January 1996 and June 2000; 65 women were treated with metformin during pregnancy and 31 women were not. Women included in the study group conceived on metformin and continued the treatment throughout pregnancy (1000–2000 mg/day). In the metformin group, there were 62 pregnancies that resulted in live births; all newborns were healthy with the exception of a case of achondroplasia; this case was not included in the meta-analysis since such a disease has a genetic etiology. In the control group, 18 pregnancies resulted in live births without major congenital malformations.

In a prospective Parallel Randomized, Double-Blind, Controlled Clinical Trial, from April 2003 to September 2003, Palomba et al. (2005b) compared the pregnancy outcome in 100 non-obese anovulatory women affected by PCOS, 45 of whom were treated with metformin (850 mg twice daily until confirmation of pregnancy), and 47 with placebo plus clomiphene. There was a significant lower rate of spontaneous abortion in the metformin-exposed group compared with the control one. No malformations were observed in 28 metformin-exposed pregnancies and 10 control pregnancies during the 9-month follow-up. Palomba and collaborators published several other papers on trials evaluating pregnancy outcomes of women exposed to metformin prior to or during the first trimester of pregnancy; all of these publications were excluded from the meta-analysis since there was overlap with other studies or because data on birth defects were lacking (Palomba et al., 2004, 2005a, c, d, 2006, 2007, 2009a, 2010, 2011a, b).

Moll et al. (2006) performed a randomized double-blind clinical trial, from June 2001 to May 2004, comparing the efficacy of clomiphene plus metformin (500–2000 mg/day) and clomiphene plus placebo in women with PCOS. The metformin-exposed group was made up of 114 women, while the control one was made up of 11 women. In the first group metformin was taken until a positive pregnancy test. In the metformin-exposed group there were 14 ongoing singleton pregnancies that were excluded from the meta-analysis. The remaining pregnancies resulted in 13 spontaneous abortions, 29 live births, 3 perinatal deaths (triplets delivered at 17 gestational weeks); two cases with congenital anomalies were observed (one with Kartagener’s syndrome and hypospadias; one with anal atresia). Since Kartagener’s syndrome is a genetic diseases and hypospadias has been described in affected patients, this case was not included in the estimation of the birth defects rate for the meta-analysis.

In the control group there were 11 ongoing pregnancies. The remaining pregnancies resulted in 12 spontaneous abortions, 41 live births (one twin pregnancy) and 1 perinatal death of an anencephalic child who was delivered at 18 gestational weeks.

In the ‘PPCOS’ trial by Legro et al. (2007), 626 infertile women with PCOS were treated with clomiphene plus placebo, metformin plus placebo, or a combination of metformin and clomiphene. Medication was discontinued when pregnancy was confirmed. There were 105 conceptions exposed to metformin (500–2000 mg/day) that resulted in 71 live births, 30 losses during the first trimester and 4 losses during the second and third trimesters. One woman delivered a child with Prader–Willi syndrome (excluded from the meta-analysis) and another one delivered a child with a congenital diaphragmatic hernia. In the control group there were 62 conceptions that resulted in 47 live births, 14 losses during the first trimester and 2 losses during the second and third trimesters; no major malformations were observed.

Nawaz et al. (2008) conducted a case–control study from January 2005 to December 2006 to compare the pregnancy outcome of 105 PCOS-affected women who conceived while taking metformin (mean dose 1500 mg/day) with that of 32 PCOS-affected women who conceived spontaneously without metformin. In the drug-exposed group, 40 women stopped metformin between 4 and 16 weeks of pregnancy (Group A), 20 women received metformin until 32 weeks of gestation (Group B) and 45 women were treated throughout pregnancy (Group C). There were 10 miscarriages and 95 live births in the drug-exposed group, while 6 miscarriages and 26 live births in the control group. One baby whose mother stopped metformin between 4 and 16 weeks of pregnancy had polydactyly. No other congenital anomalies, intrauterine deaths or stillbirths were reported in cases and controls. Another more recent and larger study was published by the same authors in 2010 (Nawaz and Rizvi, 2010). However we did not included it in the meta-analysis since the control group also counted patients who conceived on metformin.

The double blinded multi-center randomized ‘PCOSMIC’ trial (Johnson et al., 2010) studied the pregnancy outcome of 171 anovulatory or oligo-ovulatory women (from August 2003 to February 2007); 102 women were treated with metformin (500–1500 mg/day) while 69 women were not. Metformin was stopped once pregnancy was diagnosed. There were 39 pregnancies in the metformin group resulting in 30 live births (2 multiple pregnancies), 8 spontaneous abortions prior to 20 weeks and 1 ectopic pregnancy; no major malformations were observed. In the control group there were 19 pregnancies that resulted
in 15 live births (2 multiple pregnancies), 2 spontaneous abortions prior to 20 weeks, 1 ectopic pregnancy and 1 termination of pregnancy at 23 weeks for fetal hypoplastic heart; no other major malformations were reported.

Begum et al. (2013) performed a randomized controlled trial (from December 2004 until August 2009) in which 55 women diagnosed with PCOS were given metformin and clomiphene, 55 women were given metformin and rFSH and 55 women were given only rFSH to induce ovulation. Therefore a total of 110 women were treated with metformin (1500 mg/day) and 37 of these became pregnant, while there were 16 pregnancies in the control group. Treatment was discontinued after a positive pregnancy test. Metformin-exposed pregnancies resulted in 29 live births (1 twin gestation), 4 spontaneous abortions, 3 blighted ovum and 1 ectopic pregnancy. In the control group there were 12 live births (no multiple pregnancies), 3 spontaneous abortions and 1 blighted ovum. No cases of major birth defects were reported. A previous study by the same group (Begum et al., 2009) was not selected since the recruitment period (from June 2002 until December 2006) overlapped with the present one and the control group included patients exposed to metformin until the 8th gestational weeks.

Taken individually, each study included in the meta-analysis failed to detect an increased risk of congenital malformations in the exposed group compared with the control group. However the sample size of most studies was too small for the detection of rare events such as congenital malformations.

After the meta-analysis, the rate of major birth defects in the metformin-exposed group was not statistically increased with regard to the disease-matched control group and there was no significant heterogeneity among studies. The metformin-exposed sample was composed of 351 pregnancies and the OR was 0.86 (95% confidence interval: 0.18–4.08; \( P_{\text{heterogeneity}} = 0.71; \) Fig. 3). The birth defects reported are listed in Table III.

Six studies evaluated women exposed to metformin until recognition of pregnancy (Vandermolen et al., 2001; Palomba et al., 2005b; Moll et al., 2006; Legro et al., 2007; Johnson et al., 2010; Begum et al., 2013): the rate of major birth defects in this subgroup of patients was not statistically higher than that detected in the respective control group (2/189 versus 2/128; Fisher exact test \( P\text{-value} = 1.0 \)). Glueck et al. (2001), Jakubowicz et al. (2002) and Nawaz et al. (2008, Groups B and C) evaluated the pregnancy outcome of women who were treated with metformin throughout the first trimester: no major malformations were observed in this subgroup of women and in the respective control group (0/130 versus 0/50).

**PCOS studies excluded from the meta-analysis but reporting relevant data on birth defects**

Sixteen studies were excluded from the meta-analysis because of an inappropriate control group (women exposed to metformin at the time of conception and until confirmation of pregnancy) (Batukan and Baysal, 2001; Vanky et al., 2004, 2010; Qublan and Malkawi, 2005; Thatcher and Jackson, 2006; Turner et al., 2006; Begum et al., 2009; Qublan et al., 2009; Sohrabvand et al., 2009; Nawaz and Rizvi, 2010; Ott et al., 2010; De Leo et al., 2011; Khattab et al., 2011; Liao et al., 2011; Glueck et al., 2013; Romualdi et al., 2013). The characteristics and the results of these studies are presented in Table IV, in order to estimate the overall rate of birth defects in women exposed during the first trimester to metformin.

Together with these, six out of the nine studies selected for the meta-analysis are also included; the other three studies (Glueck et al., 2001; Nawaz et al., 2008; Begum et al., 2013) were replaced by larger or more recent studies by the same groups.

The overall rate of major congenital anomalies was 1% (16 cases among 1522 pregnancies), lower than the expected rate in the general population (∼3%). Analyzing only the studies where the outcomes for different subgroups of metformin exposure were specified, 634 women were treated throughout the first trimester of pregnancy and 517 women discontinued the therapy upon conception or confirmation of pregnancy (usually before 8 weeks) (Batukan and Baysal, 2001; Vandermolen et al., 2001; Jakubowicz et al., 2002; Palomba et al., 2005b; Qublan and Malkawi, 2005; Moll et al., 2006; Turner et al., 2006; Legro et al., 2007; Begum et al., 2009; Qublan et al., 2009; Sohrabvand et al., 2009; Johnson et al., 2010; Nawaz and Rizvi, 2010; Ott et al., 2010; De Leo et al., 2011; Khattab et al., 2011; Liao et al., 2011; Glueck et al., 2013). Three major birth defects were reported in each subgroup (0.5% in pregnancies exposed throughout the first trimester versus 0.6% in pregnancies exposed until confirmation of pregnancy; Fisher exact test: \( P\text{-value} = 1 \)).

**Discussion**

Metformin is an ‘insulin sensitizer’ approved by the US Food and Drug Administration for the treatment of type 2 diabetes, but in the last decade it has been increasingly used also for the treatment of infertile

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**Figure 3** Meta-analysis of studies evaluating women affected by PCOS—Forest Plot.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Period of study</th>
<th>Metformin-exposed pregnancies</th>
<th>Outcome</th>
<th>Birth defects</th>
<th>Major birth defect rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batukan and Baysal (2001)</td>
<td>Switzerland</td>
<td>Not reported</td>
<td>15 P until confirmation of pregnancy</td>
<td>3 LOSS, 12 LB</td>
<td>None</td>
<td>0/12</td>
</tr>
<tr>
<td>Vanky et al. (2004)</td>
<td>Norway</td>
<td>October 2000–March 2003</td>
<td>18 P from 1st trimester (5–12 weeks) delivery [8 metformin at conception]</td>
<td>0 LOSS, 18 LB (1 perinatal death)</td>
<td>Only minor anomalies: 2 periauricular adnex; 1 Unilateral cryptorchidism</td>
<td>0/18</td>
</tr>
<tr>
<td>Qublan and Malkawi (2005)</td>
<td>Jordan</td>
<td>January 2001–September 2002</td>
<td>6 P from conception to 12 weeks</td>
<td>1 LOSS (Ectopic P), 1 ongoing P, 4 LB</td>
<td>None</td>
<td>0/4</td>
</tr>
<tr>
<td>Turner et al. (2006)</td>
<td>Ireland</td>
<td>Not reported</td>
<td>50 P from conception to throughout the first trimester</td>
<td>7 LOSS (1 Ectopic P), 43 LB</td>
<td>None</td>
<td>0/43</td>
</tr>
<tr>
<td>Begum et al. (2009)</td>
<td>Bangladesh</td>
<td>June 2002–December 2006</td>
<td>29 P from conception to delivery 30 P until 8 weeks</td>
<td>1 LOSS, 28 LB</td>
<td>None</td>
<td>0/28</td>
</tr>
<tr>
<td>Sohrabvand et al. (2009)</td>
<td>Iran</td>
<td>January 2004–December 2006</td>
<td>25 P until 5–6 weeks 25 P until 8 weeks</td>
<td>1 LOSS, 24 births</td>
<td>None</td>
<td>0/24</td>
</tr>
<tr>
<td>Qublan et al. (2009)</td>
<td>Jordan</td>
<td>January 2006–June 2008</td>
<td>15 P from conception to 12 weeks</td>
<td>1 LOSS, 14 LB</td>
<td>None</td>
<td>0/14</td>
</tr>
<tr>
<td>Ott et al. (2010)</td>
<td>Austria</td>
<td>January 2001–December 2008</td>
<td>120 P until confirmation of pregnancy</td>
<td>18 LOSS, 2 TOP, 100 LB</td>
<td>I anencephaly (TOP) I case excluded (Down syndrome –TOP)</td>
<td>1/(100 LB + 1 TOP)</td>
</tr>
<tr>
<td>De Leo et al. (2011)</td>
<td>Italy</td>
<td>Not reported</td>
<td>98 P from conception to delivery</td>
<td>9 LOSS, 89 LB</td>
<td>None</td>
<td>0/89</td>
</tr>
<tr>
<td>Liao et al. (2011)</td>
<td>China</td>
<td>Not reported</td>
<td>8 P until confirmation of pregnancy</td>
<td>1 LOSS, 7 LB</td>
<td>None</td>
<td>0/7</td>
</tr>
<tr>
<td>Khattab et al. (2011)</td>
<td>Egypt</td>
<td>August 2004–January 2008</td>
<td>160 P stop at conception or at 8 weeks 200 P from conception to delivery</td>
<td>0 LOSS, 160 births 0 LOSS, 200 LB</td>
<td>None</td>
<td>0/160</td>
</tr>
<tr>
<td>Glueck et al. (2013)</td>
<td>USA (Ohio)</td>
<td>1997–2012</td>
<td>76 P from conception to delivery</td>
<td>14 LOSS, 62 LB</td>
<td>I tracheo-esophageal fistula I sacrococcygeal teratoma</td>
<td>1/200</td>
</tr>
<tr>
<td>Romualdi et al. (2013)</td>
<td>Italy</td>
<td>Not reported</td>
<td>55 P from 1st trimester (5–12 weeks) delivery</td>
<td>8 LOSS, 47 LB</td>
<td>None</td>
<td>0/47</td>
</tr>
</tbody>
</table>
6 studies included in meta-analysis\textsuperscript{x}.

<table>
<thead>
<tr>
<th>70 LOSS (1st – 3rd trimester), 224 LB</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 cases excluded: (1 Prader–Willi syndrome, 1 achondroplasia, 1 Kartagener’s syndrome + hypospadias)</td>
</tr>
<tr>
<td>2/221</td>
</tr>
</tbody>
</table>

\textsuperscript{x} The more recent and larger study by the same group (Bolton et al., 2009) has not been selected because it was confined to all women treated with metformin who delivered a baby weighing 500 g or more in the three-year period 2003 – 2005 [66 pregnancies with 2 cases with Ventricular Septal Defects, 2/66 (3%)].

\textsuperscript{a} From July 21, 1997 to May 22, 2006, there was only one case with major birth defects (Sacrococcygeal teratoma). Another study (Ramidi et al., 2009) was excluded because of a possible overlap with the present one (26 P + metformin, 22 LB, 4 LOSS; one neonate with tethered spinal cord).

\textsuperscript{b} Seven women with PCOS type 2 diabetes (no insulin therapy).
carriers, with a higher transfer rate from the fetal to the maternal side (Kovo et al., 2008b; Hemauer et al., 2010; Terti et al., 2010).

The majority of the published studies with women affected by PCOS have been designed to evaluate the ovulation, pregnancy and spontaneous abortions rates and when the follow-up continued until delivery, the live birth rate was reported without any information regarding the detection of birth defects.

The present meta-analysis, evaluating 9 controlled studies with 351 pregnancies exposed to metformin in the first trimester, supports the hypothesis that metformin is not a major teratogen [OR = 0.86 (95% confidence interval: 0.18–4.08)]. However, it is important to note that the control group is small; this is a consequence of the characteristics of the trials, which were designed to study the rate of ovulation and pregnancy, and the effect of metformin on them: the actual number of women who ovulated and became pregnant was higher in the study group than in the control group. Moreover, approximately half of the women discontinued the treatment upon confirmation of pregnancy and part of them could have been exposed only during the so-called ‘all or nothing’ period, when the embryo continues its normal development if the damaged cells are replaced by other totipotent cells or it is aborted if too many cells are damaged or killed.

Nevertheless, the rates of anomalies in both the subgroup of women who were treated with metformin throughout the first trimester and the subgroup of women who were treated until a positive pregnancy test were not statistically higher than the rates of anomalies in their own respective control groups. In addition, these results are further supported by our analysis of all the published, non-overlapping studies reporting details of the congenital anomalies observed in the offspring of women exposed to metformin during pregnancy. In fact the rate of congenital anomalies was very low both in the sample of 517 women who discontinued the therapy upon conception or confirmation of pregnancy and the sample of 634 women who were treated with metformin throughout the first trimester of pregnancy (0.6 versus 0.5%).

However, several important limitations in this analysis do not allow definitive conclusions to be drawn. First of all, the quality of data is limited due to extrapolation from studies which were not specifically designed to evaluate the rate of congenital defects. Second, the samples were relatively small, highly selected and non-homogeneous in terms of treatment protocols for infertility, duration of treatment, obesity and glycemic control. In addition no detailed information on any other medications taken during pregnancy and on terminations of pregnancy was reported. The possibility of a significant selection bias is also suggested by the low rate of malformations observed in this analysis, lower than the one shown for the general population. Finally, the wide confidence intervals of the Odds Ratios do not allow a significant teratogenic effect to be excluded.

The interpretation of the studies involving type 2 diabetic women is more complex since the risk of birth defects is increased by the maternal diabetes itself and it is often difficult to distinguish whether a malformation is a consequence of the disease or the pharmacologic therapy. In fact, the incidence of birth defects and other adverse outcomes including fetal death, macrosomia and preterm delivery among the offspring of type 2 diabetic mothers is higher than among the infants of non-diabetics (Mathiesen et al., 2011). With our search strategy, we were unable to identify a sufficient number of studies with metformin exposure during the first trimester to proceed with the meta-analysis. Moreover, in many cases glycemia was poorly controlled and there was often a high rate of perinatal deaths which may have affected the rates of anomalies. Thus, the lack of adjustment for the glycemic control in most studies does not allow any conclusions to be drawn about the possible teratogenic effect of metformin.

Several studies and meta-analyses regarding metformin therapy during the second and third trimesters have been published; most of these studied the efficacy of metformin in the management of gestational diabetes, that is diagnosed in ~3–7% of pregnancies and it is associated with an increased risk of several adverse outcomes for both the mother and the offspring (Kjos and Buchanan, 1999; Jovanovic and Pettitt, 2001). The detection and the appropriate treatment of gestational diabetes can reduce both maternal and fetal morbidity (Crowther et al., 2005; Langer et al., 2005). Most women can be treated satisfactorily with a diet alone, while a minority require treatment with oral hypoglycemic therapies or insulin to achieve a proper metabolic control. The available data suggest that metformin is as effective as insulin in controlling gestational diabetes and preventing complications, especially in case of mild gestational diabetes (Moore et al., 2007; Terti et al., 2008, 2013; Balani et al., 2009; Dhulkotia et al., 2010; Goh et al., 2011; Ijas et al., 2011; Gandhi et al., 2012; Niromanesh et al., 2012; Corbould et al., 2013; Gui et al., 2013; Hickman et al., 2013; Lautatiz et al., 2013; Magedfagin et al., 2013; Spauloni et al., 2013; Waheed et al., 2013); however the heterogeneity of these studies, their often small sample size and the differences between treatment groups do not allow firm conclusions to be reached on the risks and benefits of metformin. In addition, the rate of cases needing additional insulin to reach euglycemia was particularly high in one study (Rowan et al., 2008).

In conclusion, human experience with metformin during the first trimester of pregnancy is reassuring but specific studies designed ad hoc for the evaluation of its teratogenicity are warranted in order to demonstrate the safety of this drug in pregnancy. The teratology information services (Clementi et al., 2002), collecting prospective data on women exposed to drugs during pregnancy, may play an important role in the evaluation of the embryo-fetal effects of metformin.

Authors’ roles

M.C. was responsible for the conception and design of the study; contributed substantially to the acquisition, analysis and interpretation of data; prepared, drafted and revised the article critically for important intellectual content; and approved the final draft for publication. M.D. contributed substantially to the acquisition, analysis and interpretation of data; prepared, drafted and revised the article critically for important intellectual content; and approved the final draft for publication. E.D.G. and P.L. prepared, drafted and revised the article critically for important intellectual content; and approved the final draft for publication. M.D. contributed substantially to the acquisition, analysis and interpretation of data; prepared, drafted and revised the article critically for important intellectual content; and approved the final draft for publication. E.D.G. and P.L. prepared, drafted and revised the article critically for important intellectual content; and approved the final draft for publication. M.D. contributed substantially to the acquisition, analysis and interpretation of data; prepared, drafted and revised the article critically for important intellectual content; and approved the final draft for publication. E.D.G. and P.L. prepared, drafted and revised the article critically for important intellectual content; and approved the final draft for publication.

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Conflict of interest

None declared.
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Metformin in pregnancy and birth defects


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