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Short running title: Oral contraception in girls with type 1 diabetes

Corresponding author

Dr. biol. hum. Barbara Bohn, MPH

Institute of Epidemiology and Medical Biometry, ZIBMT

University of Ulm

Albert-Einstein-Allee 41

D-89081 Ulm, Germany

Telephone: +49 731 5025483 Fax: +49 731 5025309

E-Mail: barbara.bohn@uni-ulm.de

Original Research: Oral contraception in adolescents with type 1 diabetes and its association with cardiovascular risk factors. A multicentre DPV study on 24,011 patients from Germany, Austria, or Luxembourg.

Authors Barbara Bohn, PhD^{1,13,*}, Kirsten Mönkemöller, MD^{2*}, Dörte Hilgard, MD³, Axel Dost, MD⁴, Karl Otfried Schwab, PhD⁵, Eggert Lilienthal⁶, Elke Hammer, MD⁷, Kathrin Hake, MD⁸, Maria Fritsch, MD⁹, Bettina Gohlke, PhD¹⁰, Carine de Beaufort, PhD^{11,12}, Reinhard W. Holl, PhD^{1,13} on behalf of the DPV-initiative

¹ Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm,
89081 Ulm, Germany

²Department of Paediatrics, Kinderkrankenhaus Amsterdamer Straße, 50735 Cologne, Germany

³ Department of Paediatrics, Gemeinschaftskrankenhaus Herdecke, 58313 Herdecke, Germany

⁴ Department of Paediatrics, University Hospital Jena, 07747 Jena, Germany

⁵ Department of Paediatrics and Adolescent Medicine, University Medical Centre, 79106 Freiburg, Germany

⁶ Department of Paediatrics, University of Bochum, 44801 Bochum, Germany

⁷ Department of Paediatrics, Katholisches Kinderkrankenhaus Wilhelmstift, 22149 Hamburg, Germany

⁸ Children's Hospital, Müritzklinikum Waren, 17192 Waren (Müritze), Germany

⁹ Department of Paediatric and Adolescent Medicine, Medical University of Vienna, 1090 Vienna, Austria.

¹⁰ Department of Paediatric Endocrinology and Diabetology, University Hospital Bonn, 53127 Bonn, Germany

¹¹ Department of Paediatrics, Centre Hospitalier Luxembourg, 1210 Luxembourg, Luxembourg

¹²,Department of Paediatrics, University Hospital Brussels, UZB, 1090 Brussels, Belgium

¹³ German Centre for Diabetes Research (DZD), 85764 Munich-Neuherberg, Germany

*shared first authorship

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Abstract

Objective: To investigate differences in cardiovascular risk factors and metabolic control in girls with type 1 diabetes with or without use of oral contraceptives (OC) from the multicentre “diabetes prospective follow-up” registry (DPV).

Methods: 24,011 adolescent girls (13-<18 years of age) from Germany, Austria or Luxembourg with type 1 diabetes from the DPV registry were included in this cross-sectional study. Multivariable regression models were applied to compare clinical characteristics (HbA_{1C}, blood pressure, serum lipids, BMI) and lifestyle factors (smoking, physical inactivity, alcohol consumption) between girls with or without OC use. Confounders: Age, diabetes duration, and migration background. Statistical analysis: SAS 9.4.

Results: In girls with type 1 diabetes and OC use, clinical characteristics and lifestyle factors were less favorable compared to non-users. Differences were most pronounced for the prevalence of dyslipidemia (OC-users: 40.0% vs. non-users: 29.4; $p<0.0001$) and the number of smokers (OC-users: 25.9% vs. non-users: 12.5%; $p<0.0001$). OC use, sociodemographic characteristics and lifestyle factors explained between 1%-7% of the population variance in serum lipids and blood pressure. The use of OC explained a small additional proportion in all variables considered (<1%).

Conclusions: OC use in adolescent girls with type 1 diabetes was associated with a poorer cardiovascular risk profile. Biological risk factors were partly explained by a clustering of sociodemographic and lifestyle factors with a small additional contribution of OC use. Prescription of OC should therefore be combined with a screening for cardiovascular risk factors and targeted education.

Keywords: type 1 diabetes, adolescent health, oral contraception, cardiovascular risk, lifestyle

Introduction

Oral contraceptives (OC) are commonly used by adolescent girls to prevent unwanted pregnancies, but they may be also prescribed to treat acne, dysmenorrhea, or amenorrhea [1, 2]. In women with diabetes, unplanned pregnancies can pose a major health risk for both the women and the unborn child [3, 4]. Poor glycaemic control before and during pregnancy increases the risk of congenital malformations, spontaneous abortion, or fetal death [3–5]. The use of OC as one option to avoid unplanned pregnancies is recommended by international guidelines [2, 6]. In addition to concerns about vascular safety, subjects with diabetes have to deal with uncertainties regarding adverse effects of OC use on the occurrence or progression of microvascular complications (e.g. retinopathy or nephropathy) [4, 7]. However, studies conducted in adult women with diabetes showed that newer OC (with lower estrogen levels and newer progestogens) are not associated with adverse effects on metabolic control, weight gain, or the progression of microvascular complications [4, 8–12]. A Cochrane review of four randomized controlled trials found conflicting results on the influence of OC use on lipid metabolism [9]. Macrovascular complications (thromboembolic incidents or visual disturbances) were analyzed in one study [13]. No adverse effects were reported but this could be explained by the short study duration (six months) [13]. In case control and cross-sectional studies, a higher risk for stroke or myocardial infarction was reported in adult women with or without diabetes comparing OC-users to non-users [14–18]. Whether the use of OC has a stronger impact on cardiovascular risk in subjects with diabetes compared to the general population is rarely reported.

In female adolescents, studies analyzing adverse effects of OC use are sparse [19–21]. For German adolescents (13–<18 years of age), results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) indicated a slightly worse cardiovascular risk profile and an unfavorable lifestyle in OC-users compared to non-users [21]. Whether these associations are also present or even stronger in adolescent girls with type 1 diabetes is unknown.

Contraception is an important consideration in adolescent girls with type 1 diabetes [2]. Routine diabetes care should include education on potential risks of unplanned pregnancies and appropriate methods of contraception. However, several studies reported that adolescents with type 1 diabetes feel badly informed, and that risky behaviour (as smoking, alcohol consumption, or physical inactivity) increases during the late teen years [8, 22–25].

The aim of this cross-sectional study was to examine the association of OC use and metabolic control or cardiovascular risk factors/behaviour in adolescent girls with type 1 diabetes from the German/Austrian/Switzerland/Luxembourg “diabetes prospective follow-up” (DPV) registry.

Methods

Data source and subjects

The study population for the present analysis was selected from the multicentre DPV registry. Currently, 445 specialized diabetes centres from Germany (n=409), Austria (n=34), Switzerland (n=1), and Luxembourg (n=1) prospectively document demographic and clinical data of patients with any type of diabetes. Semi-annually, participating DPV centres transfer locally collected and pseudonymized data to the University of Ulm, Germany, for central analysis and quality assurance. In case of inconsistency or implausibility, data are reported back to the centres for verification or correction. Ethical approval of the DPV initiative has been obtained from the ethics committee of the University of Ulm. Data collection has been approved by the local/national review boards of each participating centre.

From the year 1995 to March 2017, 464,967 patients with diabetes were documented in the database. For the current analysis, female adolescents (13-<18 years of age) with type 1 diabetes were included (n=24,011). Due to missing information on OC use, girls from Switzerland were excluded (n=5). For each patient, the most recent year of treatment was analyzed. In case of multiple data sets per patient, data were aggregated. Variables were aggregated as median (e.g. HbA_{1c}), as cumulative sums (e.g. severe hypoglycaemia), or as maximum (e.g. smoking). Patients were stratified according to the use of oral contraceptives (OC) (Fig. 1). The data set included combined OC (containing both estradiol and progestin) as well as progestin-only pills. The DPV registry does not provide detailed information on the ethinyl-estradiol (EE) dosage or the progestin content; all types of OC (including progestin-only pills) were therefore summarized as “OC use”.

Outcome variables

Sociodemographic characteristics

Age, diabetes duration, and migration background (defined if at least one parent or the child itself was born outside from Germany/Austria) were considered. Living in new/old federal states of Germany was also analyzed since disparities between new federal states of

Germany (former German Democratic Republic, “East Germany”) and old federal states of Germany (former Federal Republic of Germany, “West Germany”) are possible. Although health status of adolescents has been become more similar since the German reunification in the year 1990, some important differences remain [26]. Compared to their peers living in old federal states of Germany, regular alcohol consumption, smoking or physical inactivity are more common in adolescents from new federal states of Germany [26].

Clinical data and treatment modalities

HbA_{1c}, serum lipids, systolic and diastolic blood pressure, body mass index (BMI), rates of severe hypoglycaemia (with or without coma) or diabetic ketoacidosis (DKA), hospital admission, self-monitoring of blood glucose (SMBG), daily insulin dose/kg bodyweight (BW), and use of insulin pumps were analyzed. HbA_{1c} was mathematically standardized to the reference range of 20–42 mmol/mol (Diabetes Control and Complication Trial: 4.05–6.05%) by applying the multiple-of-the-mean transformation method [27]. Severe hypoglycaemia was defined as an event requiring assistance by another person to actively administer carbohydrates, glucagon, or other resuscitative actions. DKA was diagnosed in subjects with a pH-value <7.3 or hospital admission due to DKA. BMI was calculated as the ratio of the body weight in kilograms and the squared body height in metres (kg/m²) and was expressed as standard deviation score (SDS), using data from a nationally representative sample of German adolescents [28]. Adolescents with a BMI ≥90th percentile were characterized as overweight using reference data of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) [28]. Hypertension was defined by increased levels of systolic and/or diastolic blood pressure (≥95th sex-specific percentile of the KiGGS study, which simultaneously accounted for age and height) [29] or by the use of antihypertensives. Dyslipidemia was defined by at least one elevated value of total cholesterol, LDL cholesterol, triglycerides (≥95th percentile, respectively) and/or decreased levels of HDL cholesterol (<5th percentile) [30], or by the use of lipid-lowering drugs.

Lifestyle factors

At each visit to the physician, the DPV software requires information about lifestyle factors. Questions on lifestyle include smoking (yes/no), alcohol consumption (yes/no) and physical activity (yes/no). All information were based on patient self-reports to their diabetes-care teams.

Statistical analysis

Sociodemographic characteristics were presented as median (Q1; Q3), or as percentage (%). To compare differences between girls with or without OC, Chi square (χ^2) test was used for dichotomous variables and Kruskal–Wallis test for continuous variables. The false discovery rate was applied to correct p-values for multiple comparisons. Multiple regression models were created for differences in clinical characteristics and lifestyle factors between adolescent girls with or without use of OC. Linear regression models were conducted for continuous variables (BMI, HbA_{1C}, daily insulin dose/kgBW, SMBG/day, systolic/diastolic blood pressure, total cholesterol (C), LDL-C, HDL-C, triglycerides) and logistic regression models for categorical variables (HbA_{1C} >7.5% (58.5mmol/mol), overweight, hypertension, dyslipidemia, smoking, alcohol consumption, physical inactivity). Negative binomial regression was implemented for the rate of severe hypoglycaemia or DKA per 100 patient-years (PY), and hospital admissions per 1 PY. All models were adjusted for age, diabetes duration, and migration background. Treatment centre was included as a random effect in order to adjust for between-centre variation. Since smoking is also associated with unfavorable metabolic control, lifestyle, and OC use [31, 32], a further regression model was conducted including smoking (yes/no) as an additional confounder.

To analyze the relative contribution of OC use to the differences in biological cardiovascular risk factors (systolic blood pressure, diastolic blood pressure, total cholesterol (C), LDL-C, HDL-C, and triglycerides) between patient groups, multiple linear regression models were implemented. Model 1 was adjusted for age, diabetes duration, region (new/old federal states of Germany), migration background, overweight, physical activity, smoking, and

alcohol consumption. Model 2 contained variables of model 1 and the use of OC. To ensure a comparison of the results of our type 1 diabetes population with that of a recently published cohort from the German KiGGS study [21], only adolescents from Germany (~95% of the whole study population) were considered and treatment centre was not included in the regression models.

A two sided p-value <0.01 was considered significant. All statistical analyses were implemented with SAS 9.4 (Statistical Analysis Software, SAS Institute, Cary, NC, USA).

Results

The study population comprised 24,011 female type 1 diabetes patients with a median age of 16.8 (Q1: 15.1; Q3: 17.4) years and a median diabetes duration of 6.4 (Q1: 3.5; Q3: 9.7) years. A migration background was documented in 14.4% of the patients. Of all girls included, 94.5% (n=22,705) were from German DPV centres, 5.0% (n=1,192) from Austrian DPV centres, and 0.5% (n=114) from Luxembourgian DPV centres. The use of OC was reported in 14.0%. Stratified by country, the proportion of OC users varied between 10% (Austrian) and 15% (Germany/Luxembourg). OC use increased by age ($p<0.0001$). The lowest use was found in 13 year olds (0.8%), the highest OC use was present in 17 year olds (21.4%). Over the last two decades, the number of girls with type 1 diabetes and OC use remained stable ($p=0.35$). OC users were older, had a longer diabetes duration, and a migration background was less frequently reported compared to non-users (Table 1).

Clinical and lifestyle differences between OC-users and non-users

Results of regression models (adjusted for age, diabetes duration, and migration background) revealed a higher prevalence of cardiovascular risk factors in girls with OC use compared to non-users (Table, 2, Fig. 2). The percentage of girls with dyslipidemia was higher in OC-users compared to non-users (40.0% vs. 29.4%; $p<0.0001$). Regarding single values of serum lipids, greatest differences were present in total cholesterol and in triglycerides (both $p<0.0001$; Table 2). Differences in the proportion of patients with overweight were negligible ($p=0.11$). An $\text{HbA}_{1\text{C}} >7.5\%$ (58.5mmol/mol) was more prevalent in OC-users (Fig. 2). In girls with type 1 diabetes and OC use, smoking, physical inactivity, and alcohol consumption were more frequent compared to non-users (all $p<0.0001$; Fig. 2). Further differences between patients with or without OC use are illustrated in Table 2.

After additional adjustment for smoking, the percentage of subjects with an $\text{HbA}_{1\text{C}} >7.5\%$ (58.5mmol/mol) (69.6% vs. 68.5%; $p=0.29$) or being physically inactive (62.5% vs. 61.1%; $p=0.26$) were comparable between OC-users and non-users. No differences in BMI SDS (0.49 vs. 0.47; $p=0.15$), SMBG per day (4.6 vs. 4.7; $p=0.095$), or the rate of DKA per 100PY

(3.9 vs, 3.3; $p=0.11$) were observed when smoking was additionally adjusted for. Results of other variables considered did not change (data not shown).

Contribution of OC use on population variance of biological cardiovascular risk factors

Linear regression models indicated that between 1% to 7% of the population variance in biological risk factors (systolic and diastolic blood pressure, total cholesterol (C), LDL-C, HDL-C, and triglycerides) can be explained by sociodemographic characteristics, behavioural risk factors, and OC use (Table 3, Model 1). The use of OC explained a small additional proportion of the population variance in all biological risk factors considered (<1%, respectively) (Table 3, Model 2).

Discussion

In this large cross-sectional DPV study we examined differences in clinical characteristics and lifestyle factors between type 1 diabetes girls with or without the use of oral contraceptives (OC). Overall, cardiovascular risk factors were more prevalent in OC-users compared to non-users. Differences were most pronounced for the prevalence of dyslipidemia and for the proportion of smokers.

Sociodemographic differences between OC-users and non-users

Out of all female adolescents with type 1 diabetes from the DPV registry, OC use was documented in 14.0%. In our DPV study population, the proportion of girls with a migration background was substantially smaller in OC-users compared to non-users (8.7% vs. 15.3%, $p < 0.0001$). The lower number of girls with a migration background is still comparable to previous findings for Germany as for example from the German KiGGS study (6.5% vs. 19.3%) [21] or published data from the Federal Centre for Health Education (BzgA; Bundeszentrale für gesundheitliche Aufklärung) [33]. Female teenagers with migration background who reported to be sexually active are older and prefer alternative methods of contraception compared to girls without migration background. This is most likely due to cultural or religious beliefs, as most immigrating families in Germany have an Islamic background with families not supporting sexual activity of their daughters [33].

Girls with type 1 diabetes and OC use were older compared to non-users (17.3 vs. 16.6 years of age; $p < 0.0001$). The use of OC increased by age from 0.8% in 13 year olds to 21.4% in 17 year olds ($p < 0.0001$) which is consistent with survey data showing that most girls from Germany reported their first sexual intercourse with the age of 17 years or later [33]. Results from the German KiGGS study confirmed the increasing OC use in older girls [21]. They reported an increase from 0.2% in 13 year olds to 45.6% in 17 year olds [21]. Overall, prevalence of OC use of the general population was higher compared to the DPV type 1 diabetes population (DPV: 14% vs. KiGGS: 19.6%) [21]. Studies including adult women with type 1 diabetes also reported a lower OC use compared to the general

population [34]. In British women (15-44 years of age) with type 1 diabetes, OC were less frequently prescribed (25.1%) by the general practitioner compared to an aged matched healthy control group (29.5%) [34]. There are several explanations for the lower OC use in our study population. In adolescents with type 1 diabetes, social (e.g. leaving the parental home) and physical adulthood (e.g. bone age, or pubertal onset) can be delayed compared to their peers without diabetes [35, 36]. This could lead to a later onset of sexual activity. In addition, both under-reporting and under-documentation of OC use in the electronic health record system cannot be excluded. There is some evidence that teenagers and women with type 1 diabetes feel uninformed on contraception and tend to practice unsafe non-pharmacologic contraception methods [22, 25, 34]. Moreover, one main barrier to prescribe or to use OC is the concern about adverse metabolic and cardiovascular effects [4, 8–13].

Clinical and lifestyle differences between OC-users and non-users

Overall, biological cardiovascular risk factors and an unhealthy lifestyle were more frequently documented in female adolescents with type 1 diabetes and OC use compared to non-users (Fig. 2; Table 2). Most distinct differences between patient-groups could be observed in the modifiable risk factors dyslipidaemia (40.0% vs. 29.4%) and smoking (25.9% vs. 12.5%). Our results are in line with findings on healthy adolescents reporting an association of OC use and biological cardiovascular risk factors or an unfavourable lifestyle [19, 21, 37]. In particular smoking poses an additional cardiovascular risk and further increases the chance for thromboembolism in OC users. The risk of stroke or venous thromboembolism is rather low in adolescents with OC use. However, there is evidence that cardiovascular risk factors and an unhealthy lifestyle (smoking, physical inactivity) increase with age and often track from childhood to adulthood [25, 38–40]. Minimizing cardiovascular risk factors in order to prevent early atherosclerosis is therefore one of the main goals in paediatric diabetes care. It is imperative to record atherogenic risks and integrate their management into diabetes care.

Regarding metabolic control, the percentage of girls with an elevated HbA_{1c} >7.5% (58.5mmol/mol) was slightly higher in OC-users compared to non-users (71.2% vs. 67.9%;

$p=0.0005$). OC with ethinyl-estradiol (EE) doses below 35µg do not influence glycaemic control [8]. Over the past 10 years, OC containing high doses of EE have been rarely prescribed for adolescents in Germany [41]. Differences in HbA_{1c} levels are therefore more likely due to other effects such as behavioural differences. Smoking seems to be associated with worse metabolic control and an unhealthy lifestyle behaviour [31, 32]. This finding can be confirmed by our study. Within the group of smokers, the proportion with an HbA_{1c} >7.5% (58.5mmol/mol) was 85%, whereas in non-smokers, the percentage of girls with an HbA_{1c} >7.5% (58.5mmol/mol) was 66%. Similar to previous findings, no association between OC use and overweight prevalence was observed in our study population [19].

Contribution of OC use on population variance of biological cardiovascular risk factors

Aside sociodemographic and behavioural factors, the use of OC showed a small additive effect on blood pressure and serum lipids in girls with type 1 diabetes (Table 3) which is in agreement with findings for adolescents of the general German population [21]. The study of Du and colleagues reported a relative contribution of OC use on biological cardiovascular risk factors between less than 1% in systolic and diastolic blood pressure to 1-6% in serum lipids [21] which is higher compared to our results (<1.0%, respectively). The effect on lipid metabolism depends on the oestrogen dosage and the progestin component. Data on OC and lipid profiles in adolescents are sparse. In a small prospective study with 33 adolescents, the association between OC use (EE 30µg, progestin 75µg) over 3 years and serum lipids was investigated [42]. Although serum values remain within a normal range, a significant increase in triglycerides, total cholesterol, LDL-C, but also in HDL-C was found [42]. A Cochrane review on OC use in adults with type 1 and 2 diabetes indicated conflicting results on lipid metabolism in three small studies [9].

Clinical implications

Diabetologists and other health professionals working with adolescents with diabetes tend to focus on other aspects of diabetes care without addressing sexual health or discussing

possibilities of contraception [43]. In addition, it is assumed that the responsibility for contraception counselling is unclear between diabetes teams, gynecologists and paediatricians. At the same time, adolescent girls may be reluctant to bring up the topic of contraception by themselves. Our study supports the recommendations of ISPAD [2] and WHO [6] to include the use of OC in contraception counselling by supporting the safety of OC in adolescents with type 1 diabetes. The initial clinical assessment should focus on comorbidities such as thrombogenic mutations, dyslipidaemia, hypertension and macro- or microangiopathy [6]. As modifiable atherogenic risk factors predominate, targeted education should be included in the treatment. Monitoring of blood pressure and dyslipidaemia are to be ensured.

Strength and Limitations

This population-based analysis benefits from its large number of female adolescents with type 1 diabetes. To our best knowledge, this is the first study investigating associations between the use of OC and cardiovascular risk factors in girls with type 1 diabetes. A limitation of this study is that data entry on the use of OC in the electronic health record system is not mandatory. Hence, under-documentation of OC use cannot be excluded. Furthermore, in clinical settings, minors are often interviewed in the presence of their parents. Therefore potential under-reporting of OC use, smoking, or alcohol consumption need to be mentioned. Unfortunately, we cannot provide any data on different OC: neither the EE dosage was reported, nor the progestin content. In addition, progestin-only preparations are put together with the classical EE/progestin combination pill in this study. Therefore, it was not possible to conduct a stratified analysis by OC of different generations. Another shortcoming is that clinical characteristics were not available from all patients included. Moreover, due to the cross-sectional design of this study, observed associations cannot prove causal effects.

Conclusion

In conclusion, this cross-sectional study indicated a higher prevalence of modifiable cardiovascular risk factors and a worse metabolic control in female adolescents with type 1 diabetes and OC use compared to non-users. Differences were most pronounced for the prevalence of dyslipidaemia and smoking. Relative contribution of OC use on atherogenic risk factors was negligible compared to the impact of sociodemographic characteristics and lifestyle factors (smoking or physical activity). Overall, the benefits of OC use, such as protection from unplanned pregnancy, seem to outweigh potential adverse effects in girls with type 1 diabetes. Addressing contraception needs is important for adolescent girls with type 1 diabetes and should be combined with a screening for cardiovascular risk factors and targeted education.

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Figure Legends

Fig 1: Selection of study population

Fig 2: Differences in cardiovascular risk factors and lifestyle factors between type 1 diabetes subjects with or without use of OCs

Fig 1

Fig 2