Use of the Levonorgestrel Intrauterine Device in Women with Type II Diabetes Mellitus

Benjamin Lang

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Masters of Public Health

University of Washington

2017

Committee:
Sarah Prager
Elizabeth Micks

Program Authorized to Offer Degree:
School of Public Health
Department of Health Services

University of Washington

Abstract

Use of the Levonorgestrel Intrauterine Device in Women with Type II Diabetes Mellitus

Benjamin Andrew Lang

Chair of the Supervisory Committee:
UW Associate Professor Sarah Prager MD, MAS
Department of Obstetrics and Gynecology

OBJECTIVE: To determine the safety, effectiveness, and impact on glycemic control of the levonorgestrel-releasing intrauterine device (LNG-IUD) among women with type II diabetes.

STUDY DESIGN: We conducted a retrospective chart review of women diagnosed with type II diabetes who had an LNG-IUD placed within the University of Washington Medical Center system between 2007 and 2012. We abstracted and analyzed the patient demographics, indications for placement, complications, and changes in glycemic control as measured by hemoglobin A1c before and after placement.

RESULTS: We identified 115 women under the age of 55 with type II diabetes who had an LNG-IUD placed during the study period. The mean age was 37.2 years and the mean weight was 252.2 pounds. Fifty-seven percent were using the LNG-IUD primarily for contraception, while 30.4% were using it primarily to treat heavy menstrual bleeding. There were no documented pregnancies with the LNG-IUD in place. Expulsions were noted in 3.5% of women. Adverse effects included abdominal or pelvic pain in 13.9%, and pelvic inflammatory disease (PID) in 1.7% of women during the study period. Thirty-nine patients had A1c data before and

up to 2 years after placement, and there was no significant change in A1c (mean A1c decrease of 0.17, CI -0.76 to +0.43).

CONCLUSION: The LNG-IUD appears to be safe and effective in women with type II diabetes, with few complications and no significant effect on glycemic control.

1. Introduction

The prevalence of type II diabetes has more than doubled worldwide over the last three decades and incidence continues to increase.[1] Pregestational type II diabetes increases the risk of maternal perinatal mortality and complications[2] and may lead to neonatal complications, including major congenital malformations, spontaneous abortion, and macrosomia.[3–5] Given the significant risks of type II diabetes to both maternal and neonatal health, it is particularly important that women with type II diabetes have access to safe and effective contraception. The purpose of this study is to assess the safety and effectiveness of the levonorgestrel-releasing intrauterine device (LNG-IUD) in women with type II diabetes.

The World Health Organization[6] and the CDC[7] assign a category 2 rating for the LNG-IUD in type II diabetes. A category 2 denotes that the advantages of using the contraceptive method generally outweigh the theoretical or proven risks for the given medical condition. A systematic review in 2013 concluded that there was very limited evidence for the safety and effectiveness of the LNG-IUD in type II diabetics[8]. However, some experts have suggested that the category 2 rating for the LNG-IUS in women with diabetes may be overly cautious.[9] To our knowledge, there has been no new research on the topic since that time.

The lack of data on the LNG-IUD for patients with type II diabetes may contribute to differences in clinical care. Women with diabetes are less likely to be offered highly effective reversible contraception and more likely to undergo sterilization procedures than healthy patients.[10] In conversations about contraception, providers may recommend less effective non-hormonal methods[11,12,13] or methods with lower user satisfaction,[14] putting these patients at higher risk of unintended pregnancies. Finally, women with diabetes may particularly benefit from noncontraceptive effects of the LNG-IUD, such as treatment for heavy menstrual bleeding,

the prevention and treatment of endometrial hyperplasia and prevention of endometrial cancer,[15] conditions for which women with diabetes are at increased risk.[16]

Studying the safety and effectiveness of the LNG-IUD among women with type 2 diabetes is especially important given the limited contraceptive options available to these women. Estrogen-containing hormonal contraceptives (including the oral contraceptive pill, transdermal patch, and vaginal ring) have been found to increase the risk of thrombosis and cardiovascular disease. These estrogen-containing contraceptives have been assigned a category 3/4 rating by the CDC for diabetic women with vascular disease, indicating that they should generally not be used among this population.[17] Depot medroxyprogesterone acetate (DMPA), a progestin-based contraceptive, has also been assigned a category 3 by the CDC for diabetic women with vascular disease due to evidence that it may negatively disrupt cholesterol, lead to weight gain, and increase the risk of thrombosis.[7]

In healthy women, the LNG-IUD is highly effective and very safe.[18] We expect the same to be true for women with type II diabetes due to low systemic absorption of the progestin hormone in the LNG-IUD.[19] Furthermore, while DMPA has been associated with negative effects on cholesterol, weight gain, and thrombosis, the same has not been found for other progestin-based contraceptives, including the LNG-IUD.[20,21] Furthermore, a small case series of 11 women with type II diabetes using the LNG-IUD found little or no influence on glycemic control in their 12 months of follow up.[22] Our hypothesis is that the LNG-IUD is safe and effective in women with type II diabetes, and does not affect glycemic control.

2. Methods

We conducted a retrospective chart review of all women previously diagnosed with type II diabetes who had an LNG-IUD placed at the University of Washington between January 1, 2007 and March 1, 2012. This study used similar methods to a study by Vu *et. al.* on long-acting reversible contraception (LARC) among patients with cardiovascular conditions at the University of Washington during the same time period.[23] The University of Washington Institutional Review Board approved this study. Microsoft Amalga Unified Intelligence System was used to extract data from the electronic medical records from the University of Washington Medical Center, Harborview Medical Center, and other University of Washington affiliated clinics. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Washington.[24] Subjects were identified using ICD-9 codes for type II diabetes and related complications, as well as procedure and pharmacy codes for LNG-IUD placement. All charts were individually reviewed to confirm accuracy of the electronic extraction. Two researchers independently reviewed a subset of charts in duplicate and compared results to confirm congruence between reviewers.

Subjects were excluded if they were over 55 years of age or using the IUD for postmenopausal indications. Hemoglobin A1c laboratory data was included in the analysis if a patient had an A1c value within 3 months before to 10 days after LNG-IUD placement and had an A1c value 3 months to 24 months post placement while the device was still present. These time constraints were chosen as the A1c value demonstrates glycemic control over the prior 3-month period and these criteria adequately reflect blood sugar levels before and after LNG-IUD placement. We excluded hemoglobin A1c data for those who were having an LNG-IUD replacement or switching from another form of hormonal birth control to remove the possibility of effects on glycemic control of pre-placement pharmacological hormones. We compared mean

values of hemoglobin A1c pre- and post-IUD placement to determine if there was a significant change in glycemic control using a simple hypothesis test of a mean. We analyzed patient characteristics, indications, and complications following LNG-IUD placement and compared to population means using one sample tests for proportions. All analyses were performed in Stata 14.

3. Results

We identified 115 women under the age of 55 with type II diabetes who had an LNG-IUD placed during the study period. The characteristics of this patient group are outlined in Table 1. The majority of women in this study had multiple medical comorbidities. The IUD placements that occurred in the operating room were primarily in the context of dilation and curettage or hysteroscopy procedures. Five percent of the LNG-IUD devices were placed within one week post-abortion, and 20% were placed within 6 weeks postpartum.

Four subjects (3.5%) experienced IUD expulsion, sixteen (13.9%) had a subsequent clinic visit in which they reported abdominal or pelvic pain, and two (1.7%) were diagnosed with pelvic inflammatory disease. One of the expelled IUDs was placed at a 6 week postpartum visit while the other 3 occurred after interval placements.

No patient became pregnant with an IUD in place, however one patient had a presumed luteal phase IUD insertion, with negative urine pregnancy test at the time of IUD placement. Ten weeks after IUD placement, she was found to be pregnant at an estimated gestational age of 12 weeks. This subject underwent a surgical abortion and replacement of the IUD. One subject became pregnant after spontaneous IUD expulsion and 3 became pregnant after their IUD was removed due to pain or bleeding.

Thirty-nine patients had hemoglobin A1c lab data both before and after IUD placement per criteria described in our methods. With a mean A1c at time of placement of 8.5 (range 4.3-14.6) and a mean A1c post-placement of 8.48 (range 4.3-14.6), these patients exhibited no significant change in A1c after LNG-IUD placement during the mean follow up time of 287 days (mean decrease of 0.17%, CI -0.76 to 0.43%). The 10 patients who had their IUD placed postpartum had a nonsignificant increase in their A1c of 1.35% (95% CI of -0.02 to 2.7%). The 29 patients with interval placement had a mean decrease of 0.24% (95% CI of -1.06 to 0.57%). Of the 9 patients using insulin at time of placement in this group, there was also no significant difference with a mean increase of 0.87% (CI of -1.19 to 2.95%).

After IUD placement, 6% of patients had new diagnoses of kidney disease, 6% had diagnoses of neuropathy, 2.6% had diagnoses of retinopathy, 2.6% had new diagnoses of vascular disease, and one patient began using insulin. Most women (77.5%) were still using the IUD at the end of the study period, with a mean follow up time of 754 days.

4. Discussion

This case series provides evidence that LNG-IUD use in women with type II diabetes is safe, effective, and does not affect glycemic control. Women with type II diabetes using the LNG-IUD experience side effects and complications at rates comparable with published data in nondiabetic women.[20] The rates of complications of diabetes seen in this population are similar to those noted in other studies of patients with type II diabetes.[25]

There were several limitations of the study. This is a retrospective case series without a nondiabetic comparison group. Additionally, our subjects were all from one academic medical center, tended to be older, and had more medical comorbidities than many of the typical patients

using the LNG-IUD for contraception, all of which could limit generalizability. However, this population represents a diverse group of patients with type II diabetes using the LNG-IUD and the study demonstrated safety and effectiveness that is in line with population data.

Furthermore, the size of our study was limited, particularly for the group in which we examined pre- and post-IUD placement hemoglobin A1c data. Only 39 patients met our criteria of having an A1c value within 3 months before to 10 days after LNG-IUD placement and an A1c value 3 months to 24 months post placement while the device was still in place. Our criteria for which patients' A1c data were used to calculate changes in glycemic control excluded a large number of patients with glycemic data but allowed us to more to more accurately measure the temporal effect of the LNG-IUD on blood sugar.

Finally, as this was a case series, we cannot determine whether patients were lost to follow up or seen for complications at other healthcare facilities, nor how patients' glycemic control may have been influenced by factors such as changes to medication or lifestyle. As the University of Washington Medicine system is a large network that includes inpatient and outpatient care throughout the area, it is unlikely that many women were lost to follow up.

Despite these potential limitations in generalizability and available data, our study represents the largest retrospective case series to date examining type II diabetics and the LNG-IUD. This study helps to fill an existing gap in the literature and demonstrate that the LNG-IUD appears to be safe and effective in the type II diabetic population. Several studies have shown that women with diabetes are less likely to receive prescriptions for contraceptives[10] even though pregnancy among these women carries an increased risk of maternal and fetal complications.[2] Given the high satisfaction and continuation rates of the LNG-IUD among the general population,[14] and the evidence provided in this study that the LNG-IUD is safe and effective in

women with type II diabetes, the LNG-IUD should be considered a first-line contraceptive option for women with type II diabetes.

References

1. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. *Nat Rev Endocrinol*. 2012;8(4):228-236. doi:10.1038/nrendo.2011.183.
2. Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care*. 2005;28(2):323-328. doi:10.2337/diacare.28.2.323.
3. Ylinen K, Aula P, Stenman UH, Kesäniemi-Kuokkanen T, Teramo K. Risk of minor and major fetal malformations in diabetics with high haemoglobin A1c values in early pregnancy. *Br Med J (Clin Res Ed)*. 1984;289(6441):345-346.
4. Pedersen JF, Molsted-Pedersen L, Mortensen HB. Fetal growth delay and maternal hemoglobin A1c in early diabetic pregnancy. *Obs Gynecol*. 1984;64(3):351-352.
5. Shakya Hua Zhang S, Zhang H. Over-and Undernutrition Gestational Diabetes Mellitus and Macrosomia: A Literature Review. *Nutr Metab*. 2015;66(2):14-20. doi:10.1159/000371628.
6. World Health Organization. *Medical Eligibility Criteria for Contraceptive Use, 5th Edition*. Geneva, Switzerland; 2015. http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf. Accessed May 2, 2016.
7. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep*. 2016;65(3):1-103. doi:10.15585/mmwr.rr6503a1.
8. Goldstuck ND, Steyn PS. The Intrauterine Device in Women with Diabetes Mellitus Type

I and II: A Systematic Review. *ISRN Obstet Gynecol*. 2013;2013:814062. doi:10.1155/2013/814062.

9. Allen RH, Cwiak CA, eds. *Contraception for the Medically Challenging Patient*. New York, NY: Springer New York; 2014. doi:10.1007/978-1-4939-1233-9.
10. Schwarz EB, Postlethwaite D, Hung Y-Y, Lantzman E, Armstrong MA, Horberg MA. Provision of Contraceptive Services to Women with Diabetes Mellitus. *J Gen Intern Med*. 2012;27(2):196-201. doi:10.1007/s11606-011-1875-6.
11. Isaacs JN, Creinin MD. Miscommunication between healthcare providers and patients may result in unplanned pregnancies□. *Contraception*. 2003;68:373-376. doi:10.1016/j.contraception.2003.08.012.
12. Trussell J. Contraceptive failure in the United States. *Contraception*. 2011;83:397-404. doi:10.1016/j.contraception.2011.01.021.
13. Winner B, Peipert JF, Zhao Q, et al. Effectiveness of long-acting reversible contraception. *N Engl J Med*. 2012;366(21):1998-2007. doi:10.1056/NEJMoa1110855.
14. Peipert JF, Zhao Q, Allsworth JE, et al. Continuation and satisfaction of reversible contraception. *Obstet Gynecol*. 2011;117(5):1105-1113. doi:10.1097/AOG.0b013e31821188ad.
15. Kim JJ, Chapman-Davis E. Role of progesterone in endometrial cancer. *Semin Reprod Med*. 2010;28(1):81-90. doi:10.1055/s-0029-1242998.
16. Carlson MJ, Thiel KW, Yang S, Leslie KK. Catch It Before It Kills: Progesterone, Obesity, and the Prevention of Endometrial Cancer. *Discov Med*. 2012;14(76):215-222.
17. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ*. 2009;339:b2890.

doi:10.1136/bmj.b2890.

18. Espey E, Ogburn T. Long-acting reversible contraceptives: intrauterine devices and the contraceptive implant. *Obstet Gynecol*. 2011;117(3):705-719. doi:10.1097/AOG.0b013e31820ce2f0.

19. Nilsson CG, Lahteenmaki PL, Luukkainen T, Robertson DN. Sustained intrauterine release of levonorgestrel over five years. *Fertil Steril*. 1986;45(6):805-807. http://www.ncbi.nlm.nih.gov/pubmed/3086130. Accessed November 28, 2016.

20. Berenson AB, Rahman M, Wilkinson G. Effect of injectable and oral contraceptives on serum lipids. *Obstet Gynecol*. 2009;114(4):786-794. doi:10.1097/AOG.0b013e3181b76bea.

21. Attia AM, Ibrahim MM, Abou-Setta AM. Role of the levonorgestrel intrauterine system in effective contraception. *Patient Prefer Adherence*. 2013;7:777-785. doi:10.2147/PPA.S36948.

22. Grigoryan O, Grodnitskaya E, Andreeva E, et al. Contraception in perimenopausal women with diabetes mellitus. *Gynecol Endocrinol*. 2006;22(4):198-206. doi:10.1080/09513590600624317.

23. Vu Q, Micks E, McCoy E, et al. Efficacy and Safety of Long-Acting Reversible Contraception in Women With Cardiovascular Conditions. *Am J Cardiol*. 2016;117(2):302-304. doi:10.1016/j.amjcard.2015.10.026.

24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2008;42:377-381. doi:10.1016/j.jbi.2008.08.010.

25. Fonseca VA. Defining and Characterizing the Progression of Type 2 Diabetes. *Diabetes Care*. 2009;32:151-156. doi:10.2337/dc09-S301.

Table 1: Patient characteristics

Patient characteristics	
Total Patients, N	115
Age, mean ± SD (range) years	37.1 ± 9.26 (16-55)
Age groups, N (%)	
Age <18	1 (0.87)
Age 18-35	45 (39.1)
Age 35-55	69 (60)
Weight, mean ± SD (range) pounds	252.2 ± 82.0 (133-461)
BMI, mean ± SD (range)	42.8 ± 12.7 (19.8-82.6)
Nulligravid, N (%)	18 (15.6)
Nulliparous, N (%)	27 (23.4)
Insurance status, N (%)	
Private	43 (37.4)
Public	54 (46.9)
Self Pay	7 (6.1)
Unknown	11 (9.6)
Indication, N (%)	
Contraception	65 (56.5)
Menorrhagia	47 (40.9)
Pain treatment	2 (1.7)
Cancer prophylaxis	1 (0.9)
Time of placement, N (%)	
Interval clinic visit	51 (44.4)
Operating room	30 (26.1)
Postpartum	23 (20)
Vaginal delivery	9 (7.8)
Caesarean Section	14 (12.2)
Post abortion	6 (5.2)
Replacement	5 (4.3)
Diabetic control before LNG-IUS placement, N(%)	
Concurrent hypertension	68 (59.1)
Long term use of insulin	16 (13.9)
Diabetic eye disease	8 (6.9)
Renal complications	5 (4.3)
Vascular insufficiency	3 (2.6)
Neuropathy	4 (3.4)