Contraceptive Use in Women with Inherited Metabolic Disorders: A Retrospective Study and Literature Review

Jessica Gold (goldj@email.chop.edu)
Childrens Hospital of Philadelphia https://orcid.org/0000-0002-6210-4214
Nina B Gold
Massachusetts General Hospital
Diva D DeLeon
Childrens Hospital of Philadelphia
Rebecca Ganetzky
Childrens Hospital of Philadelphia

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Abstract

Background

Reproductive planning is an emerging concern for women with inherited metabolic disease (IMD). Anticipatory guidance on contraception is necessary to prevent unintended pregnancies in this population. Few resources exist to aid informed decision-making on contraceptive choice. A retrospective case-control study was performed to examine trends in reproductive planning for adolescent and adult women seen at the Children's Hospital of Philadelphia (CHOP). Literature review on contraception and IMD was performed to assess global use.

Results

In a cohort of 221 reproductive-aged female IMD patients, 29.4% reported routine contraceptive use. Anticipatory guidance on contraception was provided by metabolism doctors to 36.8% of patients during the study period. Contraception discussion was more likely to occur in women older than 21 years, who lived independently and were followed by gynecology. Women who received contraception counseling from their metabolism provider were 40-fold more likely to use regular contraception. Use of combined hormonal contraceptives was most commonly reported, but contraception choice varied by age and IMD.

Conclusion

Metabolism providers are ideally suited to provide guidance on contraception to women with IMD. Reproductive planning should be addressed routinely using shared decision-making. Contraceptives should be selected for their efficacy, effects on metabolism, and likelihood of patient adherence.

Background

Due to expanded newborn screening and medical advancements in care and diagnosis, people with inherited metabolic disorders (IMD) are surviving into adulthood with improved health. As these individuals age, there is a growing need for counseling on reproductive care.[1,2] For many women with IMD, pregnancy carries risks both to the patient and to the developing fetus, particularly if the pregnancy is unintended and the underlying IMD is inadequately managed. Some hormonal contraceptives may disrupt metabolism, leading to adverse outcomes. As such, counseling on contraceptive selection is important for women with IMD. Because patients with IMD often have long-lasting and frequent contact with their metabolism providers, these clinicians are well-positioned to facilitate anticipatory guidance discussions on reproductive care.

The World Health Organization (WHO) has published guidelines for contraception in the setting of common medical disorders, including liver disease, hypertension, and diabetes. No centralized

information on best practices for women with rare diseases, including IMD, exists. Contraceptives vary widely in their efficacy, mechanism of action, usage, and side effects. For women with medical comorbidities, it is critical to balance the risks of any contraceptive method with the adverse outcome of an unintended pregnancy.[3,4] This study and review of the literature aims to examine trends in reproductive planning for women with IMD at one center and propose considerations for counseling on contraceptive selection.

Results

The Metabolism section at CHOP followed 221 reproductive-aged females, including 111 adolescents 12-21 years old, and 110 adults 22-50 years old between January 2012 and December 2019. Most adolescent patients live with a parent or caregiver (93%), while half of the adult patients live independently (50.9%). Intellectual disability (ID) has been diagnosed in 37.1% of our cohort, affecting 41.4% of adolescents and 32.7% of adults.

A metabolism provider documented counseling about contraception use during at least one visit with 36.8% of reproductive-aged patients. Discussions were significantly more likely to occur with patients who were adults (OR 3.3, CI 1.9-5.9), live independently (OR 3.1, CI 1.7-5.7), or are followed by gynecologists (OR 5.93, CI 3.24-10.8) (Fig. 1). The presence of ID did not significantly affect introduction of this topic. Routine contraceptive use was reported by 29.4% of patients, including 20.7% of adolescents and 38.9% of adults (Fig. 1). Contraception use was significantly higher in adult patients (OR 2.6, CI 1.4-4.6), patients living independently (OR 4.23, CI 2.3-7.9), and patients seeing gynecologists (OR 3.43, CI 1.88-6.26). Most notably, contraceptive use was 40-fold more likely in patients who received anticipatory guidance from their metabolic provider. Counseling on contraception by a metabolism provider led to initiation of use within 2.37±1.3 visits.

Combined hormonal contraceptives (CHC), including the pill, patch, and vaginal ring were most commonly used (Fig. 2A). Long-acting reversible contraception (LARC), including reversible forms (IUD or progesterone implant) and surgical methods, was more likely to be used by adults compared to adolescents (OR 6.46, CI 1.33-31.3). We also examined use of contraception according to underlying metabolic diagnosis (Fig. 2B). Current and historic forms of contraception were included. Contraception use varied among IMD class. Patients with lysosomal storage disorders, specifically Gaucher disease, were most likely to use contraception, with the majority opting for CHCs or surgical methods. Of note, no patient in our cohort with homocystinuria or a hepatic glycogen storage disorder (GSD) had ever used a CHC, which is contraindicated in these disorders.[5–7]

Many patients at high risk for adverse events during pregnancy were not using contraception. Most patients with urea cycle disorders (UCD) and organic acidemias did not report contraception use (65% and 68% respectively). Among patients with phenylketonuria, 77% had never had the use contraception documented, despite consensus recommendations.[8] Anticipatory guidance regarding pregnancy and phenylketonuria (PKU) was not universally provided. Discussion on the risks of uncontrolled PKU in

pregnancy only occurred for 30% of adolescent patients and 66.7% of adult patients. Only 25% of patients on pegvaliase and 40% of patients on eliglustat reported contraceptive use, despite it being a prerequisite for these medications.

Literature Review

Review of literature on IMD and contraception primarily revealed case reports. There is no comprehensive resource on contraceptive use, efficacy, or adverse events in IMD. Guidelines on homocystinuria, GSD I and III, and Wilson disease provided the most specific recommendations. Estrogen-containing contraception is contraindicated in homocystinuria due to the risk of thrombosis and stroke.[9] Estrogen-containing contraceptives are also discouraged in hepatic GSD due to their connection to the formation and growth of hepatic adenomas.[7,10,11] Ethinyl estradiol may increase triglycerides, a concern in hepatic GSD, and familial hyperlipidemias.[7,11,12] Copper-containing IUDs are discouraged in Wilson disease due to theoretical copper absorption. In practice, the amount of copper absorbed daily from an IUD is PKU encouraged contraceptive use without providing a preferred methods.[8,15–17] We compiled contraception recommendations for specific IMDs based on the literature reviewed (Table 1).

Discussion

Reproductive health planning is an emerging, crucial issue for people with IMDs. Contraception limits risks to patients with IMD and their offspring, as it allows for adequate reproductive planning and early pregnancy monitoring. Contraception is therefore a necessary component of the healthcare of adults and adolescents with IMD.

Contraception counseling was most likely to occur with adult women who live independently. These women are likely to attend visits independently or with a partner, avoiding the potential discomfort of addressing sexual health in front of parents or caregivers. Adult women living independently may demonstrate higher career focus making them more likely to use contraception to delay pregnancy.[18] Gynecology referral had a positive impact on contraceptive use. LARC have the lowest failure rate and were used significantly more frequently in females followed by gynecologists (with gynecology: 9/81; without gynecology: 4/121, $p<0.04$). Co-management with gynecology allows for a greater range of contraceptive options.

Diagnosis of ID had an equivocal effect on both contraception counseling and use of contraception. This runs counter to current literature on sexual health in women with ID, where the presence of ID decreases the likelihood of reproductive planning.[19] Metabolism providers may be uniquely suited to have such conversations with patients with ID because of strong rapport with patients and their families due to longstanding patient-doctor relationships. For our cohort with ID, there was no significant benefit of gynecology consultation on contraceptive use (OR 2.45, CI 0.86-6.96, $p=0.092$). In contrast, metabolism provider-led counseling on contraception significantly improves actual usage among women with ID and IMD (OR 4.8, CI 1.46-15.8, $p=0.01$) Most women with ID in our cohort opted for daily oral contraception,

such as POP or OCP (73%), and only one patient chose a LARC (IUD). We speculate that these women are already taking several daily medications and, therefore, are not burdened by adding additional daily oral medications. It is also possible that there is insufficient awareness about LARC in this population or limited options for placement.

For all cohorts, metabolism providers are well-poised to initiate conversations about reproductive health. In our clinic, engaging women even once about reproductive planning led to a 40-fold increase in contraceptive use (Fig. 1). Patients were more likely to initiate contraception on the advice of their metabolism provider compared to their gynecologist. In our clinical experience, patients with IMD frequently defer to their metabolism provider for advice on any new medication or supplement. This highlights the critical role that the metabolist plays in encouraging contraception.

Unfortunately, overall contraceptives were used only by a minority of patients across all classes of IMD, increasing the risk for unintended pregnancy (Fig. 2). This was true even in conditions where pregnancy was associated with high risk for adverse pregnancy outcomes. Only 23% of women with PKU have ever used contraception, with slightly higher percentages for female patients with organic acidemias (32%) and UCDs (35%). This resulted in an unacceptably high rate of maternal PKU syndrome (1/12 pregnancies), which causes irreversible neurologic damage to the fetus. These data are similar to those found in other studies showing that reproductive health is often omitted from healthcare transition planning [20] In general, women with chronic diseases are less likely to use contraception, despite the risks of unintended pregnancy.[21,22]

One barrier to universal metabolic counseling on contraception is the lack of systematic resources. In the IMD literature, most recommendations are provided on an *ad hoc*, case report basis. Contraception was addressed in 14.3% (12/84) of clinical practice guidelines (Table 2). The lack of expert opinion minimizes the importance of reproductive health counseling and fails to provide guidance for metabolic physicians. Misperceptions may exist about sexual activity in patients with IMD, especially those that are evaluated in a pediatric context or who still live with a caregiver, and providers may feel discomfort discussing this topic with patients whom they have known since childhood.[23] Counseling through educational hand-outs or inclusion of questionnaires in the electronic health record could lead to uniform guidance on contraception. Likewise, incorporation of healthcare contracts may encourage contraceptive use prior to starting potentially teratogenic medications, such as pegvaliase and eligustat. Similar processes, for example the iPledge program for isoretinol use, have shown efficacy in preventing unintended pregnancy in analogous contexts.[24]

This study is limited by the setting of our cohort. CHOP is a stand-alone children's hospital. It is not affiliated with an adult hospital. The Section of Metabolic Disease at CHOP follows all-aged patients (currently newborn to 88 years-old). Adults with disorders of intermediary metabolism continue to be admitted to CHOP for metabolic crises and other emergent care. There are six attending physicians within the section, all of whom are trained in pediatrics and clinical genetics. Adults are frequently seen by their childhood metabolism provider. Potential barriers include lack of experience in discussing or providing

contraception, limited knowledge on contraceptive options, scant training on offering adult-centered care, and discomfort with shared decision-making. Our cohort, with only 30% contraceptive use, may not be generalizable to metabolism clinics specifically dedicated to adult-centered care. Metabolism providers with training in internal medicine, family medicine, or obstetrics-gynecology have a stronger background in discussing and prescribing contraception, leading to higher rates of compliance with contraceptives.

Another possibility is that reproductive healthcare is lacking throughout the practice of metabolism. Many IMD were previously thought to be life-limiting with accompanying decrease in reproductive fitness. The advent of newborn screen, novel therapeutics, and improved care has a new population of adults who require specialized management. Women with IMD require more uniformity in counseling on the adverse effects of unintended pregnancy and how contraception can ameliorate these risks. Metabolism providers can serve as leaders in this area and should not assume that discussions are better led by gynecology or primary care providers. To empower metabolism-driven discussion of contraception, we summarize important aspects of counseling on contraception for women with IMD below.

Contraceptive counseling for women with IMD

To provide optimal reproductive planning advice to women with IMD, both the efficacy of the method and the effects of sex hormones on metabolism should be considered. The WHO recommends using the contraception with the lowest failure rate in women with health risks due to unintended pregnancy (currently LARC, including the hormonal and non-hormonal IUD and the progestin implant).[3,4] Estrogen and progestin, both separately and combined as CHC are responsible for several changes to metabolism in healthy women (Table 2). Patients' PCPs or gynecologists may not consider the side effects of contraception on metabolic pathways, placing the metabolism doctor in a unique role to suggest the method most compatible with the patient's diagnosis.

IMD patients' comorbidities also play an important role in contraceptive choice. Use of CHC is contraindicated in women with a history of hypertension, cardiac disease, or stroke (21.5% of our patient cohort).[3,4] Migraines with aura, a common manifestation of mitochondrial disease and reported in 23.1% of our entire cohort, are another contraindication for CHC use due to the risk of stroke.[12] Women with a history or increased risk for venous thromboembolism due to homocystinuria, cobalaminopathies and other thrombophilic IMDs also should not receive CHC.[25,26] Women with IMD may be the recipients of solid organ transplants, including liver and kidney. Most contraceptive methods are safe to use after uncomplicated organ transplant, but CHC are contraindicated in women with acute or chronic graft rejection.[3,27] IUD have also been proven to be safe post-transplant, with no increased risk of developing pelvic infections.[28] Depot medroxyprogesterone (DMPA) and IUD are preferred for women on anti-epileptic drugs due to potential medication interactions (29.4% of our cohort).[3]

Contraception may improve IMD symptoms. The guidelines for propionic acidemia/methylmalonic acidemia recommend hormonal contraception for management of perimenstrual metabolic instability.[16] Several cases of catamenial hyperammonemia in UCDs have been described, which resolved with

menstrual suppression using DMPA or CHCs.[29–31] Hormonal contraception may also limit perimenstrual aggression in Smith-Lemli-Opitz Syndrome and catamenial porphyria crises in acute intermittent porphyria.[32,33] In our cohort, 16 patients reported catamenial metabolic decompensations, of which 5 (31%) utilized hormonal contraception for management.

Discussing reproductive health with IMD patients

It is important to address surgical methods of contraception or sterilization due to its history with the eugenics movement. The United Nations convention on the rights of persons with disabilities states that "people with disabilities must have access on an equal basis to all forms of sexual and reproductive health care."[3] For women with intellectual disability, supported decision-making should occur with a trusted caregiver who will act in the best interests of the patient. Decision-makers should consider social factors, protection against sexual abuse, and support options through potential pregnancy and parenthood.[34] They should also have valid grounds for desiring sterilization, such as avoidance of grave harm from pregnancy or inability to use a reversible contraceptive. For women with IMD, consideration of the metabolic risks of pregnancy and labor must also be weighed. The popularity and effectiveness of LARCs, including the IUD and the progestin implant, may make sterilization a rarer choice.[35]

Finally, genetic counseling should occur at least once with adolescent and adult IMD patients. Counseling should address disease inheritance, recurrence risk, and options for genetic testing during antenatal and prenatal periods. Prospective parents should also be informed that variable expressivity occurs between generations for many IMD, making disease course less predictable in offspring. Additionally, discussions about reproductive health may lead to improved care coordination with patients' primary care and OB providers. These providers may need education about risks during and after pregnancy related to IMDs. Pediatricians of patients' future offspring should also be involved in care, as they may be directing the initial screening or management of newborn infants.

Conclusion

Use of contraception to prevent unintended pregnancy and catamenial exacerbation of symptoms is important for women with IMD. In our cohort, contraception counseling by a metabolism provider is the strongest predictive factor for routine contraceptive use. Metabolic providers should utilize their trusted relationships with their patients to broach discussions about reproductive health, Advice on contraceptive choice should consider the contraceptive's effects on metabolism, efficacy, comorbidities, side effects, and patient preference. CHCs have the most effects on metabolism and may not be the optimal choice for women with IMD. LARC, such as IUDs and progestin-implants, have not been studied extensively in this population, but are likely to be well-tolerated and should be considered first line. Overall, the decision regarding contraceptive use is best made on an individual basis in concert between the adolescent or adult IMD patient and her provider.

Patients And Methods

Patients. A retrospective chart review was conducted for all female patients with ages between 12-50 years-old followed by the Division of Genetics and Metabolism at Children's Hospital of Philadelphia (CHOP) (n=256). Patients with at least two visits with a clinical metabolism provider between January 2012 and December 2019 and a known diagnosis of an IMD (urea cycle disorder, fatty acid oxidation disorder, amino acidopathy, lysosomal storage disease, organic acidemia, mitochondrial disorder, glycogen storage disorder) were included. The two-visit criterion was used to ensure that only patients for whom CHOP was their established metabolic care center were included. We also excluded patients documented to be premenarchal or menopausal during the length of our study period (n=35). Demographics of our study population meeting inclusion criteria can be found in Table 3.

Statistical Analysis. Logistic regression was used to identify factors associated contraceptive counseling and use. Results were reported as odds ratios (OR) with 95% confidence intervals. All analyses were conducted using Stata 16.1.

Literature Review. We queried the PubMed and Cochrane Library databases using the following search terms: "inborn error of metabolism & contraception," "inborn error of metabolism & contraceptives," "inborn error of metabolism & birth control" "inborn error of metabolism & estrogen" "inborn error of metabolism & progesterone" "inherited metabolic disorder & contraception," "inherited metabolic disorder & contraceptives," "inherited metabolic disease & birth control" "inherited metabolic disorder & estrogen," and "inherited metabolic disorder & progesterone." This search identified 31 primary articles. We also examined 84 international clinical practice guidelines on IMD for discussion of contraception.

Abbreviations

Inherited metabolic disorders (IMD), World Health Organization (WHO), Children's Hospital of Philadelphia (CHOP), intellectual disability (ID), odds ratio (OR), confidence interval (CI), combined hormonal contraception (CHC), LARC (long-acting reversible contraception), urea cycle disorders (UCDs), phenylketonuria (PKU), lysosomal storage disorder (LSD), depot medroxyprogesterone (DMPA), intrauterine device (IUD), oral contraception pills (OCP), progestin-only pill (POP), bone mineral density (BMD), premature ovarian insufficiency (POI), glycogen storage disease (GSD), fatty acid oxidation disorder (FAOD), pyruvate dehydrogenase (PDH), Guanidinoacetate Methyltransferase (GAMT)

Declarations

Details of ethics approval: The study was approved by the institutional review board of the Children's Hospital of Philadelphia (IRB 20-017227).

Availability of Data: The datasets analyzed during the current study are available from the corresponding author upon request.

Competing Interests statement: The authors declare no potential conflicts of interest.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

Figure 1

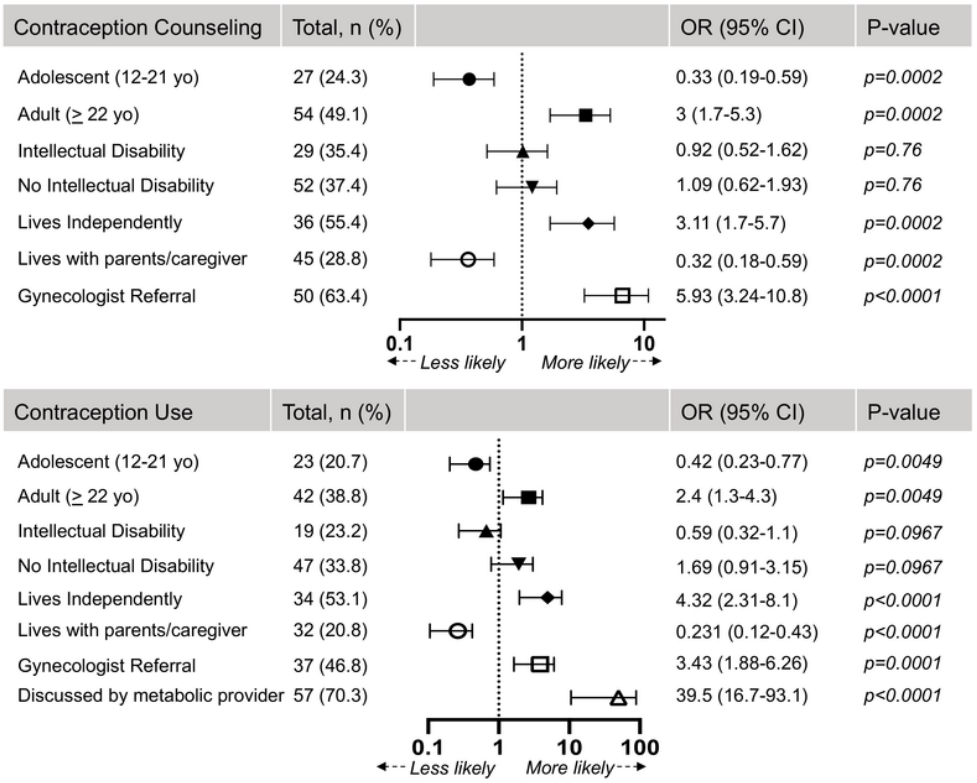

Figure 1

Counseling on contraception was significantly increased in adult patients, patients who live independently and patients who see a gynecologist. Contraceptive use was significantly increased in adult patients, patients who live independently, patients who see a gynecologist, and patients who discussed contraception with their metabolism provider. Odds ratio (OR), 95% confidence interval (CI), and p-value displayed for all categories.

Figure 2

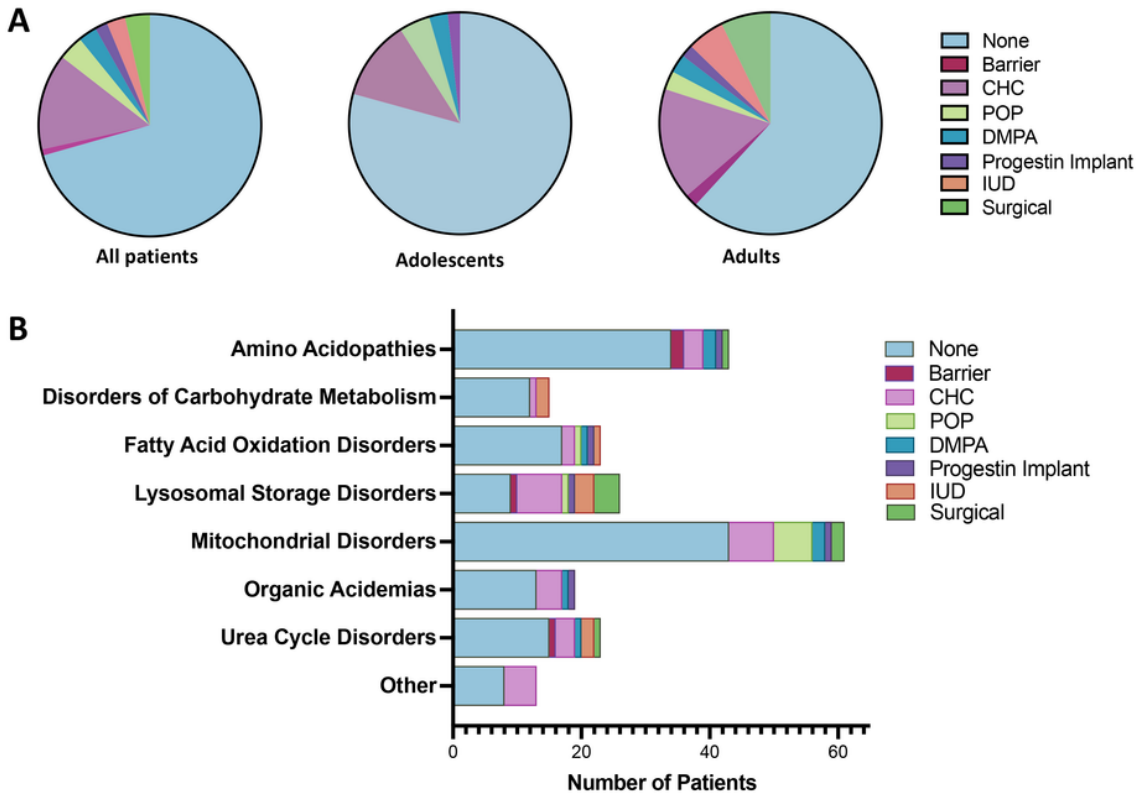

Figure 2

Contraceptive method varies by age and IMD. (A) Current documented contraceptive method in all reproductive-aged women followed by the CHOP metabolism clinic (n=221, left), adolescent women (n=111, middle), and adult (n=110, right). (B) Current and historical contraception use according to IMD diagnosis. CHC: combined hormonal contraception; POP: progestin-only pills; IUD: intrauterine device.

Supplementary Files

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- table1.png
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