Prescription medication use amongst men and women prior and during Assisted Reproductive Technologies (ART): a review

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Abstract

Along with the rising incidence of couples and individuals seeking fertility, there is an increase in the prevalence of comorbid medical conditions requiring prescription drug use. there is limited data available on medication use prior to and during artificial reproductive technology (ART) treatment and the impact these drugs may have on reproductive outcomes. This review analysed available literature on prescription medication use amongst men and women during ART, including antidepressants, anti-hyperglycaemic medications, levothyroxine and proton pump inhibitors. Further research is required to determine the prevalence of prescription drugs used during ART and assist development of standardised and informative clinical guidelines

Introduction

Medication use in pregnancy is becoming increasingly common where a 68% rise has been reported in the United States of America in the past 30 years, likely due to increasing maternal age and associated increased risk of comorbid medical conditions (1). One systematic review revealed a wide variation amongst developed countries where 27% to 93% of pregnant women were on prescription drugs excluding multivitamins. Prevalence was higher in France (93%) and lower in Northern European countries (44-47%) (2). A cohort study of 106,000 pregnancies in Norway between 2004 and 2006 found that 83% of mothers were on prescription drugs between 3 months prior to conception and 3 months after giving birth (3). On average each mother was prescribed 3.3 medications and the most common were antibiotics and respiratory medications. Furthermore 25% of fathers were on prescription drugs over the same time frame, in particular anti-inflammatory medications for musculoskeletal disease. Another study examined specific drugs used across both pregnant and non-pregnant women in United States and there was a marked age discrepancy where younger women (aged 25-34 years) were more likely to take beta blockers and non-steroidal anti-inflammatory medications whereas older women (aged 35-44 years) were more likely to be taking antidepressants and levothyroxine (*see Table 1*) (4).

Currently, nearly 3% of all babies born in the UK each year are born due to ART(5). There have been over 1,103,000 IVF cycles performed in the UK since 1991. In 2016 alone, there were over 68,000 IVF cycles, resulting in 20,028 births(6). The overall trend is that IVF cycles and births have been increasing year on year since 1991 and is projected to increase even further. The average age of women undergoing ART in the UK is 35.5, with the average age of women in natural pregnancy being 30.3 years (5, 7). Information on the prevalence of prescription drug use amongst couples undergoing ART is limited and there are even less studies available on medications taken by the male partner specifically. Importantly, paternal factors do contribute equally towards the epigenome and therefore prescription drug use in men may impact the quality of sperm, fertilisation, implantation and embryo development (8, 9).

As many patients undergoing ART are older, they may be more likely to be on more prescription medica-

tion than the rest of the child-bearing-age population. Numerous studies demonstrate common conditions that have a rising prevalence with age, including depression and/or anxiety, hypothyroidism and type 2 diabetes (10, 11). It is therefore more likely that these women will be on prescription medication for these conditions when they undergo ART. ART currently only has a success rate (defined as 'live births per ART cycle') of approximately 33% in the UK therefore it is important that any additional risks from these medications on reproductive outcomes are clarified, advising future practice and enabling couples to make an informed decision about medication use (5). Minimising the risk of failed ART and/or foetal loss but also the aforementioned teratogenic side effects of drugs is of maximal importance.

Therefore we performed this narrative review of the current evidence on prescription drug use to treat comorbid health conditions in both women and men undergoing ART. This review could then form a counselling tool for clinicians to better discuss with their patients the impact of specific medications for men and women having ART and guide clinical decision making.

Methods

This narrative review was conceived as part of an undergraduate research project between the University of Leeds and Leeds Teaching Hospitals NHS Trust. In order to determine epidemiological data on prescription drug use in ART, a search was conducted in PubMed, EMBASE and Cochrane CENTRAL register of controlled trials with the following key words: (i) 'In-vitro fertilisation',, 'ICSI (intracytoplasmic sperm injection)' 'Artificial reproductive techniques' 'ART'; and (ii) 'medications', 'therapeutics', 'drugs', 'prescription' and 'treatment' in. Papers that were written in non-English languages were not included. These results enabled us to understand the most common drugs utilised by men and women having ART and subsequently, to determine evidence of these specific drugs in a context of ART, a search was conducted independently by ER and AS with the following key words: (i) 'In-vitro fertilisation', , 'IVF', 'Artificial reproductive techniques', 'ART', 'Intra-cytoplasmic sperm injection', 'ICSI' and specific drug groups discussed below and which have been tabulated in table 2. We primarily focussed on articles which described one medication as a prescription for a pre-existing medical condition in the 6 months prior to ART treatment as the exposure, and clinical pregnancy. and live birth as the outcome. Articles, which focussed on prescription medication deliberately prescribed in order to influence ART outcome, were excluded.

Results

Anti-Depressants

There has been a rise in the use of antidepressants amongst men and women of childbearing age over the last decade. More so, patients who suffer with subfertility are vulnerable to the associated psychological and emotional sequelae associated with the diagnosis of subfertility and subsequent demanding and time-consuming process of ART, which can often exacerbate underlying mental health instability (12). Selective serotonin reuptake inhibitors (SSRI) are often first line for medical treatment of depression (13). Women are counselled in pregnancy about the risks of SSRIs including a small increased risk of persistent pulmonary hypertension in the new-born and poor neonatal adaptation syndrome (14). However, these risks are often outweighed by the potential risks of untreated depression on the pregnant woman, such as deteriorating mental health and suicide, and fetal risks, such as miscarriage, preterm labour and low birthweight(15).

One Swedish cohort study of 23,557 patients undergoing their first ART cycle over a 5-year period found that there was no statistically significant difference in ART outcomes of patient's on SSRI's, however there was a decrease in live birth rates in patients on other medications such as tricyclic antidepressants. The study lacked sufficient information on patient compliance, or whether patients were taking medication prescribed outside of the hospital environment such as in primary care or by psychiatrists working in the private sector (16). A retrospective case review of 950 patients found that patients' on SSRIs had a higher cycle cancellation rate, but no statistically significant difference in pregnancy or live birth rate (17). This study was limited by its small sample size, as well as lack of data on length of SSRI treatment. Another questionnaire-based study of over 3200 men and women found that women taking non-SSRI anti-depressants (e.g. amitriptyline) were associated with an increased risk of first trimester loss (18). However, SSRI anti-depressant use was not

associated with a statistically significant difference in first trimester loss or live birth rates. Similar results were seen in a retrospective study of 698 patients (19).

These studies suggest that there is no convincing evidence of an effect on reproductive outcomes for patients taking SSRIs prior to or during ART, however there may be some demonstrable effect on other antidepressant's such as tricyclics. Antidepressant use prior to and during ART should be considered on a case-by-case basis after careful counselling with the couple. There is an argument that mental health of patients should be optimised prior to undergoing ART, and if a patient is on SSRI's then a risk-benefit analysis of continuing the medication versus stopping it at the risk of relapse, should be carried out. Non-pharmaceutical management including cognitive behavioural therapy (CBT)) should be considered. More information on the prevalence of antidepressant use during ART including dosage, duration of treatment and associated reproductive outcomes including successful clinical pregnancy and live birth rates are required. ART can have an overwhelming, yet often overlooked, impact on the mental health of male partners too especially if investigations are associated with diagnoses of severe male factor infertility, genetic conditions with risk of vertical transmission and the potential consequence of not being able to father a child biologically resulting in the necessary use of donor sperm (20) . Further research is required on the consequences of poor mental health of male partners and the effect of antidepressant use has on associated reproductive outcomes. This will help guide clinical advice and appropriate management of these patients throughout what is often a difficult physical and emotional journey (21).

Proton Pump Inhibitors (PPI's)

Proton pump inhibitors are used primarily in the treatment of acid reflux or gastro-oesophageal reflux disease. They are commonly prescribed in general practice, with omeprazole being the only PPI licensed for use in pregnancy. However, the use of PPIs in women undergoing ART is unclear and even though use in pregnancy is generally considered safe, there is insufficient data on associated miscarriage and stillbirth rates (22). One nationwide study in Iceland found increasing rates of PPI use with age and especially amongst women therefore more information on the use of PPIs in females undergoing ART is required (23).

A cross-sectional study of nearly 22,000 people in Denmark found a roughly equal prevalence of PPI usage amongst men and women and also found that those on PPI's had higher incidences of obesity and smoking, both important factors in fertility (24). Another study found that men who had PPI treatment in the 12 to six-month period prior to ART had a 3-fold higher risk of low total mobile sperm count than those who did not, however there was no significant effect if treatment was limited to less than 6 months prior to ART (25). This study did adjust for age and other medications, however, did not take other factors into consideration such as obesity and smoking status. One theory to explain the 6-month delay is that PPI use increases gastric pH and impairs gastrointestinal absorption resulting in vitamin B deficiency. Vitamin B is essential for spermatogenesis and after 4-6 months, the resources of vitamin B become exhausted hence semen quality becomes impaired. A more recent retrospective study looked at the effect of PPI's on subfertile men and found no significant impact on semen parameters on men who were already known to have male factor subfertility (26).

Metformin

It is well-known that increased insulin resistance and associated high blood glucose levels have a great impact on menstrual cycle frequency and reproductive outcomes. Furthermore high blood glucose levels can lead to adverse pregnancy outcomes such as miscarriage, congenital malformations, stillbirth and neonatal death however, pregnancy can adversely affect maternal health leading to worsening control of diabetes and associated consequences of cardiovascular disease, retinal and renal pathology (27). As more women are delaying conception, seeking fertility treatment and/or becoming pregnant at an older age, the prevalence of type II diabetes in pregnancy is suspected to rise. Metformin is an anti-hyperglycaemic biguanide drug used commonly in the treatment of type II diabetes mellitus (28). Inhibition of hepatic gluconeogenesis and reduction of glucagon action results in reduced serum insulin and glucose concentrations, which in turn improves ovulation, pregnancy and live birth rates (29). Women with diabetes are often advised to

use metformin pre-conceptually in addition to or alternative to insulin as the benefits of improved glucose control are likely to outweigh the potential risks (30).

Diabetes Mellitus is a very common condition in the UK, and its prevalence is increasing. 1st line treatment according to the NICE guidelines for Type 2 Diabetes Mellitus is Metformin. In general, metformin is thought to be safe however there is insufficient data on its use in the first trimester and risk of miscarriage (30). Few studies have determined the effect of metformin on reproductive outcomes when used to treat diabetes. One small study of 35 women found that patients who are on metformin for diabetes had better embryo quality than patient's undergoing insulin therapy however this did not affect the implantation, clinical pregnancy or miscarriage rate (31). Metformin is also used as an ovulation induction agent in polycystic ovary syndrome (PCOS), and a Cochrane review of 42 studies (evidence range very low to moderate) concluded that metformin alone over placebo may be beneficial for live birth rates however the evidence quality was low (29). Another Cochrane review including 9 studies of moderate quality evidence, found that metformin use compared to placebo, before and after ART treatment in patients with PCOS, increased clinical pregnancy rates and reduced the risk of complications such as ovarian hyperstimulation syndrome, however there was no convincing evidence of an effect on live birth rates (32). More information on the reproductive outcomes before and during ART with use of metformin on both male and female partners is required to help guide clinical decision-making.

Levothyroxine and treatment of other thyroid disorders

Thyroid disease is associated with ovulatory dysfunction, reduced rates of conception, miscarriage and adverse pregnancy and early neonatal outcomes (33). Hypothyroidism is a disease which prevalence increases, particularly in women, as they get older (34). As with the older average age of women undergoing ART, there are more patients likely to be on levothyroxine therefore it is important to establish the safety of this drug. One retrospective study analysed reproductive outcomes of euthyroid women compared to women with hypothyroidism on levothyroxine undergoing ART and found that despite the treated group having significantly lower implantation rates, both groups had similar pregnancy rates and miscarriage rates, irrespective of age (35).

Recently, guidelines have been updated as evidence suggests that even subclinical hypothyroidism, where patients are asymptomatic and bloods tests are borderline, should be treated in order to improve reproductive outcomes for patients undergoing ART (33, 36). Chung-Hoon K et al. performed a prospective randomised control trial involving 64 patients and found that levothyroxine treatment can improve embryo quality and pregnancy outcome in subclinical hypothyroid women undergoing ART compared to those who received placebo (37).

Pelliccione F et al. performed a retrospective study on the outcomes of levothyroxine-supplemented women with subclinical hypothyroidism. They analysed 6545 cycles from 4147 women and found that there was no discernible difference between implantation or pregnancy rates between the treated and untreated women. The study did note that the benefit of levothyroxine was that it mitigated the negative effects on the thyroid axis from controlled ovarian stimulation (38).

However, a double-blinded placebo controlled multicentre trial which randomised 19585 euthyroid women with positive thyroid peroxidase antibodies and history of previous miscarriage or infertility to 50 mcg thyroxine or placebo noted no significant difference in the live birth rate or other pregnancy and neonatal outcomes (39). Patients with clinical or subclinical hypothyroidism should have thyroid stimulating hormone levels maintained at less than 2.5mU/L pre-conception (which is lower than the normal range, 0.4 to 4 mU/L, for non-pregnant women) and throughout pregnancy to optimise reproductive outcomes (40).

Hyperthyroidism is thought to affect 2.3% of women presenting with subfertility compared to 1.5% of the general population (33). Most of these women present with oligomenorrhoea or polymenorrhoea and the impact of treatment of hyperthyroidism prior to and during ART is yet to be assessed. Commonly radioiodine treatment is used in these patients and no adverse effect on gonadal function or neonatal outcomes have been noted as long as radioiodine treatment has occurred at least 6 months prior to pregnancy. Thyroid

dysfunction occurs less commonly in males compared to females however has been linked to male factor infertility. Further research is required on the treatment of thyroid disease in male partners and ART outcomes (41).

Anti-hypertensives:

Essential hypertension is thought to affect 0.6 to 2.7% of pregnancies and is more common in older populations and obese women (42). Treatment of high blood pressure is essential to reduce the risk of cardiovascular complications such as stroke and heart disease, but also to reduce the perinatal complications of pre-eclampsia, placenta abruption and intrauterine growth restriction. This literature review used the four most common classes: calcium channel blockers, ACE inhibitors, diuretics and beta blockers and found no papers on the drugs used prior to and during ART treatment effects on ART outcomes. Prevalence of hypertension is also increasing so it is important the effects of these medications are analysed, especially as there is such little data available.

Similarly essential hypertension affects almost 25% of men aged 35 to 44 years (43) and research suggests that the diagnosis of hypertension in men is associated with impaired semen quality; lower semen volume, lower sperm count and reduced motility (44). Lu et al. performed a retrospective analysis of semen results used for ART during a two-year period (1999-2001) and found no impact on sperm quality following treatment with beta blockers (45). Another study analysed high blood pressure and treatment with anti-hypertensives and their effect on semen quality (46). They found that men with hypertension were more likely to have one or more semen abnormalities compared to men without hypertension. In terms of treatment, beta blockers were associated with lower semen volume, sperm concentration and motility. There were also isolated differences observed in men taking either ACE inhibitors, Calcium Channel Blockers and Angiotensin Receptor Blockers, with diuretics providing no statistically significant differences. These studies suggests that it may be the underlying diagnosis of hypertension that leads to the sperm parameter anomalies as opposed to the medication and if the high blood pressure is well controlled, the impact on fertility is minimal (46) . However, given the results are conflicting, larger, high-quality randomised control trials are required to clarify the associations with treatment for high blood pressure and reproductive outcomes.

Asthma inhalers

Asthma is a very common condition with up to 1 in 6 adults being affected (47). It is usually well managed with inhaled beta agonists and/or inhaled corticosteroids, that have minimal systemic absorption. Despite there being several papers available for the effects of salbutamol in natural pregnancy, we were unable to identify any studies on the effect salbutamol may have on ART outcomes (48, 49). Garne et al. studied the use of anti-asthma medications (short-acting and long-acting beta agonists, and inhaled corticosteroids) in a case-control study and found that first trimester use of inhaled beta-2 agonists (salbutamol) was statistically associated with an increased risk of cleft palate, gastroschisis and renal dysplasia although the overall risk was low (48). It is not clear whether the asthma medications are associated with this risk or if it is the underlying medical condition however, no significant association was seen with the use of inhaled corticosteroids, which suggests the former. Nonetheless, uncontrolled asthma can have devastating consequences in women and therefore until sufficient evidence is available on the risks of beta-2 agonists and the risks associated with alternative medications, women are to continue treatment as per guidelines (50).

Steroids

Steroids can be used to treat a vast number of medical conditions, such as acutely for flare up of autoimmune conditions, acute asthma attacks and inflammatory bowel disease or more chronic use such as low dose steroids in cases of adrenal insufficiency. Systemic exposure to steroids has been associated with an increase in orofacial clefts in the infant, although results are conflicting, and there is insufficient data on miscarriage rates, preterm delivery and intrauterine growth restriction (51). In this review, we were unable to find any studies that analysed data on men or women taking long term steroids prior to or during ART treatment and the affect this has on reproductive outcomes. The potential unknown risks of taking these medications are often outweighed by the risk of deteriorating maternal or paternal health with associated reproductive

outcomes (52).

Heparin

Low-molecular weight heparin is used for a variety of indications, such as pulmonary embolus or deep vein thrombosis, and inherited or acquired thrombophilia (53). There are several papers that examine the use of heparin in patients who have repeated ART cycle failure to improve reproductive outcomes, however there were no papers found that examine the effect of long-term heparin therapy for comorbid medical conditions on ART outcomes.

Conclusion

Whilst prescription drug use amongst men and women of child-bearing age is common, use of individual medications is uncommon and given the ethical issues of performing randomised control trials using medications of unknown safety in pregnant women and unborn foetuses, evidence is limited to observational studies and history of previous use. Furthermore, there are some acute and or chronic medical conditions that must be treated in pregnancy to ensure overall health of the mother, father and baby. Adverse outcomes that have been reported are often rare including congenital malformations and stillbirth and therefore is difficult to determine any correlation of risk with one specific medication. As such the impact of medication exposure prior to and during ART treatments is challenging to determine. However, with more couples choosing to delay conception and hence often seek fertility treatment at an older age, couples are more likely to have comorbid medical conditions and hence be taking prescription drugs. Depression in particular is common in men and women of child-bearing age, with suicide rates rising rates amongst young men and is now the leading cause of late direct maternal death (54, 55). Couples with a history of low mood can suffer with an exacerbation of symptoms following an unexpected delay in fertility and subsequent stressful investigations and treatment. Therefore it is vitally important that we have accurate and up to date information to facilitate shared decision making in regards to continuing antidepressant treatment versus alternative non-pharmacological therapies prior to and during ART.

Health promotion through lifestyle factors including smoking cessation to target better asthma control and weight loss to reduce the rates of type II diabetes and gastric-oesophageal reflux disease may also improve patients overall health, reduce the need for prescription drug use and improve reproductive outcomes following ART.

Further research is required on prescription drug use amongst men and women and the impact on reproductive outcomes. Formal clinical guidelines are encouraged to standardise how couples are counselled and enable patients to make informed decisions about their own health and medication use during ART and throughout the pregnancy.

Disclosure of Interests

The authors declare that they have no relevant conflicts of interest, nor any interests to disclose.

Contribution to Authorship

MM and HB developed the idea for the project and designed the study. ER and AS executed the literature review and ER takes full responsibility for the papers used and references. ER drafted the manuscript with inputs and critical discussion from AS. MM and HB reviewed the manuscript once it was completed for any changes or improvements. The final version has been approved by all authors.

Details of Ethical Approval

Since this was a literature review, no specific ethical approval was required.

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25-34 Years	35-44 years
Albuterol (Short-acting beta-agonist)	Levothyroxine (thyroid hormone)

25-34 Years	35-44 years
Ibuprofen (NSAID)	Fluoxetine (SSRI) Ibuprofen (NSAID)

Table 1. Table 1 lists the most common drugs in the different age groups(4).

Prescription Medication	**Impact of maternal intake – natural conception**	**Impact of maternal/paternal intake on ART**	**Suggestion**
SSRIs	Low risk. Risk-benefit analysis. Reported increased incidence of cardio-septal defects.	No statistical difference on outcomes yet data is limited. Further research required.	Amber
PPIs	Current data suggests omeprazole is safe however limited data on other PPI's.	Negative impact on sperm if taken >6m prior to ART. Further research required to assess maternal effects.	Amber
Metformin	Considered safe; insufficient data on 1st trimester and miscarriage risk.	Beneficial in PCOS patients undergoing ART. Further research required for others.	Amber
Levothyroxine	Considered safe.	Positive effect on live birth rates in subclinical hypothyroidism. Further research required on paternal effects.	Green
Anti-hypertensives	ACEi/ARBs: proven fetal renal risk in 2nd and 3rd trimesters. CCBs: animal studies demonstrate risk but lack of data in humans. Beta-blockers: labetalol considered safe.	Further research required for maternal effects. Beta-blockers: no adverse effects on sperm quality. ACEi/ARBs, CCBs: isolated impacts on sperm Diuretics: no impact	Amber ¥
Asthma medications	Increased risk of cleft palate, renal dysplasia and gastroschisis with inhaled beta2 agonists. Inhaled corticosteroids have not been associated with adverse impacts. However, uncontrolled asthma can cause significant impacts	Further research required.	Amber (inhaled beta2 agonists) Green (inhaled corticosteroids)

Prescription Medication	Impact of maternal intake – natural conception	Impact of maternal/paternal intake on ART	Suggestion
Steroids	Further research required. Limited association with low birth weight and cleft lip/palate	Further research required.	Amber

Table 2: Summary of evidence table for impact on live birth (Red – Avoid medication use. Amber – limited evidence for medication use. Green – no known impact on live births).

¥ Red for maternal intake of ACEi/ARBs in pregnancy