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The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review

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BACKGROUND: Information regarding the possible influence of immunosuppressive drugs on male sexual function and reproductive outcomes is scarce. Men diagnosed with immune-mediated diseases and a wish to become a father represent an important neglected population since they lack vital information to make balanced decisions about their treatment.

OBJECTIVE AND RATIONALE: The aim of this research was to systematically review the literature for the influence of paternal immunosuppressive drug use on many aspects of male sexual health, such as sexual function, fertility, pregnancy outcomes and offspring health outcomes.

SEARCH METHODS: A systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE ALL via Ovid, Cochrane Central Register of Trials (via Wiley) and Web of Science Core Collection. Additionally, Google Scholar and the Clinical trial registries of Europe and the USA were searched. The databases were searched from inception until 31 August 2019. The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring health with a list of immunosuppressive drugs. Studies were included if they were published in English and if they included original data on male human exposure to immunosuppressive drugs. A meta-analysis was not possible to perform due to the heterogeneity of the data.

OUTCOMES: A total of 5867 references were identified, amongst which we identified 161 articles fulfilling the eligibility criteria. Amongst these articles, 50 included pregnancy and offspring outcomes and 130 included sexual health outcomes. Except for large Scandinavian cohorts, most of the identified articles included a small number of participants. While a clear negative effect on sperm quality was evident for sulfasalazine and cyclophosphamide, a dubious effect was identified for colchicine, methotrexate and sirolimus. In three articles, exposure to tumour necrosis factor-α inhibitors in patients diagnosed with ankylosing spondylitis resulted in improved sperm quality. The information regarding pregnancy and offspring outcomes was scant but no large negative effect associated with paternal immunosuppressive drug exposure was reported.

WIDER IMPLICATIONS: Evidence regarding the safety of immunosuppressive drugs in men with a wish to become a father is inconclusive. The lack of standardisation on how to evaluate and report male sexual function, fertility and reproduction as study outcomes in men exposed to immunosuppressive drugs is an important contributor to this result. Future research on this topic is needed and should be preferably done using standardised methods.

Key words: immunosuppressive agents / semen analysis / male infertility / sexual health / sexual dysfunction / hypogonadism / teratogenicity / pregnancy / paternal exposure / gonadal steroid hormones

Introduction

Men with immune-mediated diseases (IMDs) and a wish to become a father represent an important neglected population. The question on how they should be treated to improve (or at least not impair) their chances of achieving a successful pregnancy and a healthy offspring remains a challenge for physicians and researchers all around the world.

Based on data from Denmark, the Netherlands and Norway, it is estimated that 5.6–7.6% of fathers could be exposed to non-steroidal anti-inflammatory drugs (NSAIDs) or anti-rheumatic drugs during the pre-conceptional period (3 or 6 months before pregnancy) (Schirm *et al.*, 2004; Crijns *et al.*, 2012; Engeland *et al.*, 2013). Many factors are contributing to a substantial number of men with a wish to become a father being exposed to immunosuppressive drugs; some IMDs can affect men at a young age (i.e. juvenile idiopathic arthritis), then the prevalence of other IMDs increases during the peak of the male reproductive lifespan (i.e. rheumatoid arthritis (RA) or inflammatory bowel disease (IBD)), and furthermore in many parts of the world, men are becoming fathers at an older age (Khandwala *et al.*, 2017).

It is known that immunosuppressive drugs can affect male sexual health and reproduction via multiple mechanisms: by altering reproductive hormone secretion and/or action, by disrupting spermatogenesis or sperm motility and by causing sexual dysfunction (Sasaki *et al.*, 2011).

Furthermore, many of the available immunosuppressive drugs, such as methotrexate or sulfasalazine, were approved by the Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) before it was required to perform mandatory evaluations of male reproductive toxicity (FDA, 2015; EMA, 2017)

On the contrary, to get approval, new drugs are facing more strict protocols. Testicular toxicity is first evaluated in animal studies. When evidence suggests adverse events on the male reproductive system, complex trials in humans should follow. Importantly, in animal studies, the FDA considers histopathological evaluation to be an appropriate endpoint. In the case of human studies, semen analyses at baseline, at one spermatogenic cycle after exposure and at 13 weeks after drug discontinuation) become the most important marker of fertility. For further reassurance of testicular safety, the FDA recommends conducting randomised, double-blind, placebo-controlled, parallel-arm trials including ~200 men in a 1:1 ratio (drug:placebo) (FDA, 2015).

For men of reproductive age, the decision on which immunosuppressive drug to prescribe is not straightforward. Information regarding the possible effects on male sexual health and reproduction is still lacking for most of the commonly used immunosuppressive drugs.

The objective of our study is to provide this information in the form of a 'state of the art' systematic review. Our goal is to review the available information about the influence of paternal immunosuppressive drug exposure on many aspects of male sexual and reproductive health, such as sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes.

Methods

Protocol and registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42018096898, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=96898) and undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols (PRISMA-P) guidelines (Moher *et al.*, 2015).

Eligibility criteria

The literature search was limited to the English language and human subjects. Case–control studies, cohort studies, cross-sectional studies, case reports and case series were included. *In vitro* studies using human material were also included. Conference abstracts published after April 2016 were included. Publications without original data, such as reviews, were excluded. Publications concerning the use of immunosuppressive drugs for the treatment of any form of cancer were excluded.

The outcome data should include at least one of the following outcomes: sexual function, reproductive hormones, fertility, pregnancy outcomes or offspring outcomes. For pregnancy outcomes, publications were included if paternal exposure of immunosuppressive drugs took place in the 6 months before or around the time of conception, and in case of studies reporting sexual function or fertility parameters (i.e. semen analysis, sexual dysfunction and testosterone levels), publications were included if male exposure of immunosuppressive drugs was taken into consideration. For both categories, no restrictions were made regarding the comparison groups.

Information sources and search terms

A search strategy was developed by an experienced medical librarian (W.B.) using a structured methodology (Bramer *et al.*, 2018a,b). The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring health with a list of immunosuppressive drugs collected by experts in the fields of Rheumatology, Gastroenterology, Dermatology and Nephrology. Our full electronic search strategy is provided in Supplementary Table S1.

Subsequently, a systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE ALL (via Ovid), Cochrane Central Register of Trials (via Wiley) and Web of Science Core Collection. Additionally, Google Scholar and the Clinical trial registries of Europe and the USA were searched. We also included references from the primary search publications, in case these were missed in our search and when relevant data were missing, we contacted authors for further information. These databases were searched from inception until 31 August 2019.

Study selection and data extraction

All articles were imported into EndNote X9. After removal of duplicates with the method described by Bramer *et al.* (2016), two reviewers (L.F.P.-G. and B.t.W.) independently screened titles, abstracts and full-text of the records for eligibility. Disagreements were resolved by consensus with the help of a third reviewer (R.J.E.M.D.). Two reviewers (L.F.P.-G. and B.t.W.) extracted relevant information for each studied outcome from the included articles.

Risk of bias in individual studies

The methodological quality of the studies was assessed with the Newcastle–Ottawa Scale (NOS), developed for case–control and cohort studies (Wells *et al.*, 2013). In the case of cross-sectional studies, an adapted scale was used (Modesti *et al.*, 2016). Using these methods, points were awarded to each publication, related to the selection of the study group, the comparability of the study groups and the ascertainment of the outcomes. The score ranges from 0 to 9, with scores >5 representing good-quality studies. The results are presented in Tables I and II. Case reports were not graded. Quality assessment was done by L.F.P-G. for the sexual function, reproductive hormones and fertility data, and by B.t.W. and S.V. for pregnancy and child outcome data.

Regarding pregnancy and child outcomes data, the following 'rules' were applied. Ascertainment exposure/outcome was graded '1' (structured questionnaire equals structured interview). The question 'outcome not present at the start' was always graded '0'. Follow-up length was considered long enough for congenital anomalies if at least 1-year follow-up was reported. For long-term outcomes, the follow-up needed to last until children were 18 years of age. In cases where

Table I Summary of study characteristics and main findings for sperm quality, sexual function and reproductive hormones outcomes.

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Aminosalicylic acid and similar agents							
Di Paolo *et al.* (2001) Italy	42 (NR) NR	IBD	All sperm samples had abnormalities, mainly in motility. Sperm quality improved after stopping SSZ or switching to 5-ASA.	–	–	NR	H CS
Zelissen *et al.* (1988) The Netherlands	11 (32.3) NR	IBD	Oligospermia was detected in 72% of samples. After switching to 5-ASA, all samples showed improvement in sperm counts.	–	*	NR	L CS
Riley *et al.* (1987) UK	15 (NR) NR	IBD	Oligospermia was detected on 40% of samples. After switching to mesalazine, samples showed improvement in sperm counts.	–	NR	NR	H CS
Cosentino *et al.* (1984) USA	10 (30) 19 (NR)	IBD	Mean number of sperm count and of normal morphology was significantly lower. In five patients who stopped SSZ, improvement in sperm quality was observed.	–	*	NR	H Ch
Freixa *et al.* (1984) Spain	10 (NR) 0	Healthy participants	Prostaglandin levels in seminal plasma decreased by 36% secondary to SSZ exposure.	–	NR	NR	L CS
O'Morain *et al.* (1984) UK	39 (NR) 9 (NR)	IBD	SSZ exposure was associated with significant decrease in sperm counts, motility and increase in abnormal sperm morphology.	–	*	NR	L CC
Ragni *et al.* (1984) Italy	7 (NR) 7 (30.1)	IBD	Sperm motility was reduced in all cases and serum testosterone levels were significantly lower in exposed cases.	–	–	NR	L CC
Hudson *et al.* (1982) UK	8 (NR) 10 (NR)	IBD	Sperm head size was significantly larger in cases than in controls.	–	NR	NR	L CS

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Freeman *et al.* (1982) UK	11 (28.8) 6 (36)	IBD	Lower progressive motility in SSZ-exposed group.	–	NR	NR	L CC
Tobias *et al.* (1982) South Africa	1 (39) 0	IBD	Case report: reversible infertility after stopping SSZ, patient on high dose GCs.	–	*	NR	NA CR
Toovey *et al.* (1981) UK	28 (NR) 4 (NR)	IBD	Exposed samples showed reduced sperm motility and density and altered morphology. After withdrawal, sperm density and motility improved significantly but not sperm morphology.	–	*	NR	H CS
Levi *et al.* (1979) UK	4 (30) 0	IBD	Case series: One of the first case series where authors reported semen analysis abnormalities in SSZ-exposed patients.	–	NR	NR	NR Case series
Toth (1979) UK	6 (NR) 0	IBD	Head, midpiece and tail abnormalities were detected in spermatozoa of SSZ-exposed patients.	–	NR	NR	L CS
McIntyre and Lennard-Jones (1984) UK	3 (NR) 0	IBD	Case series: Sperm abnormalities detected after SSZ-exposed patients were sent to the infertility clinic. Sperm quality improved after switching therapy to balsalazide.	–	NR	NR	NA Case series
Iglesias-cortit *et al.* (1985) Spain	6 (NR) 0	Healthy participants	Sperm motility decreased 15% after exposure to SSZ.	–	NR	NR	L CS
Cann and Holdsworth (1984) Austria	1 (33) 0	IBD	Case report: SSZ-exposed patient who was diagnosed with infertility and achieved a successful pregnancy after switching therapy from SSZ to 5-ASA.	–	NR	NR	NA CR

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Ganatra *et al.* (2018) India	61 (NR) 0	IBD	26.23% of SSZ-exposed patients developed oligospermia. This is the first article to comment on the possible effect by disease activity.	–	NR	NR	L CS
Shaffer *et al.* (1984) UK	1 (32) 0	IBD	Case report: oligospermia associated with exposure to SSZ.	–	NR	NR	NA CR
Traub *et al.* (1979) UK	1 (25) 0	IBD	Case report: pregnancy achieved after stopping SSZ therapy.	–	NR	NR	NA CR
Chatzinoff *et al.* (1988) USA	1 (32) 0	IBD	Case report: SSZ-induced infertility case confirmed by sperm penetration assay (sperm analysis was normal).	–*	NR	NR	NA CR
Birnie *et al.* (1981) UK	21 (32.8) 0	IBD	86% of SSZ-exposed patients had abnormal semen analysis (72% had oligospermia).	–	NR	NR	L CS
Heineman *et al.* (1981) The Netherlands	2 (32) 0	IBD	Case report: reversible oligospermia in two cases exposed to SSZ. Both cases achieved pregnancies after drug withdrawal.	–*	NR	NR	NA CS
Antimalarials							
Ejebe *et al.* (2008) Nigeria	5 (NR) 10 (NR)	Healthy participants	No differences in sperm quality parameters and reproductive hormones were found between exposed and non-exposed after exposure of chloroquine 1 g/day for 2 days and then 500 mg/day for 1 day.	*	*	NR	L CS
Hargreaves *et al.* (1998) UK	NR	Healthy participants	Chloroquine had a dual *in vitro* effect, enhancing rapid motility at low concentrations but inhibiting it at higher concentrations. At 250 µg/ml chloroquine, all spermatozoa were static.	+ –	NR	NR	CS L

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Adeeko and Dada (1994) Nigeria	8 (NR) 0 (NR)	Healthy participants	Chloroquine is present in seminal plasma even after long time of no exposure.	NR	NR	NR	L Ch
Ette *et al.* (1988) Nigeria	4 (NR) 0 (NR)	Healthy participants	Chloroquine crosses the BTB, probably by passive diffusion.	NR	NR	NR	NA Case series
Calcineurin inhibitors (CsP, ciclosporine; EVE, everolimus; SIR, sirolimus; TAC, tacrolimus)							
Misro *et al.* (1999) India	NR	Healthy participants **CsP**	*In vitro* study showing that ciclosporine exerts deleterious effects on sperm, which become immotile and nonviable.	–	NR	NR	H CS
Haberman *et al.* (1991) USA	9 (41.2) NR	Kidney transplantation **CsP**	With the exemption of a low semen volume, ciclosporine A at 3 mg/kg/day did not result in other sperm quality or hormonal abnormalities.	*	*	NR	L CS
Samojlik *et al.* (1992) USA	10 (NR) 0	Kidney transplantation **CsP**	Pretreatment (pre-transplant) testosterone levels were below normal in 80%. After 12 months of treatment with CsP and other immunosuppressive drugs, testosterone levels significantly increased in all 10 cases.	NR	+	NR	L CC
Eid *et al.* (1996) Egypt	34 (32) 31 (31)	Kidney transplantation **CsP**	Sperm concentration was inversely correlated to the CsP whole blood levels.	–	*	+	H CC
Kramer *et al.* (2005) Germany	256 (NR) 0	Kidney transplantation **CsP–EVE**	Testosterone levels increased from baseline in EVE and EVE-CsP groups.	NR	+	NR	L Ch
Kantarci *et al.* (2004) Turkey	37 (38.1) 0	Kidney transplantation **CsP–TAC**	No statistical differences in baseline levels of serum FSH, LH, testosterone and PRL between CsP- and TAC-treated patients. All results were in normal ranges.	NR	*	NR	L CS
Peces *et al.* (1994) Spain	19 (35) 0	Kidney transplantation **CsP**	Serum levels of reproductive hormones were normal in CsP exposed cases.	NR	*	NR	L CS

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Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Sajad Hussain *et al.* (2015) India	1 (40)	Kidney transplantation **SIR**	Case report: patient was infertile while on Sirolimus he developed oligospermia with normal hormone levels after switching to tacrolimus he was able to conceive.	–*	*	NR	NA CR
Boobes *et al.* (2010) UAE	6 (43) 0	Kidney transplantation **SIR**	Case series: infertile patients with oligospermia, after discontinuing SRL, all patients had increased sperm counts and were able to conceive.	–*	NR	+	NA Case series
Zuber *et al.* (2008) France	25 (32) 67 (NR)	Kidney transplantation **SIR**	Sirolimus-exposed patients had lower sperm counts and motility. The fathered pregnancy rate was significantly lower in exposed patients than in non-exposed.	–	NR	NR	H CS
Skrzypek and Krause (2007) Germany	1 (29) 0	Kidney transplantation **SIR**	Recovery of spermatogenesis after cessation of sirolimus.	–*	–	NR	NR CR
Deutsch *et al.* (2007) Germany	1 (26)	Lung–heart transplantation **SIR**	Benign Leydig cell tumour in a patient exposed to sirolimus lead to testicular biopsy that showed testicular atrophy and signs of impaired spermatogenesis.	–*	–	NR	NA CR
Bererhi *et al.* (2003) France	1 (36)	Kidney transplantation **SIR**	Case report: low sperm count and motility with abnormal morphology associated with sirolimus exposure. These changes were reversed after switching therapy to tacrolimus.*	–*	NR	NR	NA
Kaczmarek *et al.* (2004) Germany	66 (NR) 66 (NR)	Heart transplantation **SIR**	Patients exposed to sirolimus had significantly lower serum testosterone levels and higher FHS/LH levels than control group.	NR	–	NR	H CS
Lee *et al.* (2005) USA	32 (41) 34 (47)	Kidney transplantation **SIR**	Patients exposed to sirolimus had significantly lower serum testosterone levels and higher FHS/LH levels than control group.	NR	–	NR	H CS

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Fritsche *et al.* (2004) Germany	28 (46.5) 28 (45.5)	Kidney transplantation **SIR**	Sirolimus daily dose and testosterone concentrations were significantly inversely correlated ($r = -0.383$).	NR	–	NR	H CC
Tondolo *et al.* (2005) USA	59 (48) 0	Kidney transplantation **SIR**	Significantly reduced levels of circulating testosterone amongst patients receiving sirolimus alone compared to those treated with calcineurin inhibitors alone were identified.	NR	–	NR	L CS
Colchicine							
Kastrop *et al.* (1999) The Netherlands	2 (40) 0	Gout	Cytogenic analysis of sperm (FISH) revealed no damage secondary to colchicine use.	*	NR	NR	NA CR
Kirchin *et al.* (1999) UK	1 (48) 0	Retinal vasculitis	Case report: reversible azoospermia.	–	NR	NR	NA CR
Sarica *et al.* (1995) Turkey	62 (32.4) 0	Behçet syndrome	The longer the use of colchicine, the more serious the adverse events on sperm count	–	+	NR	L CS
Ben-Chetrit *et al.* (1993) Israel	15 (NR) 0	Healthy participants	*In vitro* study, high concentrations of colchicine may affect *in vitro* motility of sperms, probably by its direct effect on the microtubules.	–	NR	NR	H CC
Levy and Eliakim (1977) Israel	6 (34.6) 0	FMF	After being advised to stop treatment with colchicine prior to attempt conception, sperm analysis was within normal limits in all six patients.	*	NR	NR	L CS
Bremner and Paulsen (1976) USA	7 (22) 0	Healthy participants	Colchicine caused no significant changes in sperm quality or reproductive hormones levels after 3 or 6 months of treatment.	*	*	NR	L CS
Merlin (1972) USA	1 (36) 0	Gout	Case report: azoospermia believed to be associated with colchicine use. Colchicine was stopped and after 3 months, sperm count improved and wife became pregnant.	–	NR	NR	NA CR

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Kaya Aksoy *et al.* (2019) Turkey	72 (14.5) 0	FMF	Mean colchicine dose at the time of sperm analysis was higher in patients with low sperm motility than that with normal sperm motility.	–	NR	NR	H Ch
Cyclophosphamide							
Suehiro *et al.* (2008) Brazil	13 (NR) NR	SLE	The median serum inhibin B was lower in patients treated with CYC compared with those without this therapy.	–	–	NR	L CS
Soares *et al.* (2007) Brazil	14 (NR) NR	SLE	Semen analysis demonstrated that patients who had undergone IV CYC therapy had worse sperm quality (count, motility and morphology) compared with patients who did not undergo this treatment. Elevated FSH levels were detected in patients who underwent IV CYC therapy.	–	–	NR	H CC
Anserini *et al.* (2002) Italy	19 (NR) 0	Bone marrow transplantation	10% of patients who received CYC showed azoospermia, and recovery of spermatogenesis was observed in 60% of patients.	–	NR	NR	NA Case series
Bogdanovic *et al.* (1990) Yugoslavia	17 (NA) 0	Nephrotic syndrome	Significant inverse correlation between sperm density and CYC dosage and duration of treatment.	–	NR	NR	NA Case series
Perrone *et al.* (1989) Italy	22 (NR) 20 (NR)	Nephrotic syndrome	Altered spermatogenesis was found in 41.6% of adult patients treated with CYC during childhood (1.8–5.5 mg/kg/day for 12 weeks). No significant inverse correlation of total dose of the drug with sperm density.	–	–	NR	H CC
Watson *et al.* (1985) Canada	30 (22) 18 (28)	Nephrotic syndrome	A significant inverse correlation was evident between sperm density and CYC dosage. Recovery of sperm count after prolonged interval after treatment is possible.	–	–	*	L CC

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Ogata *et al.* (1982) Japan	6 (NR) 0	Nephrotic syndrome	Histologic oligospermic changes were observed in three patients treated with high doses (10.6–16.2 g during 125–432 days).	–	NR	NR	L Case series
Fukutani *et al.* (1981) Japan	31 (33) 33 (NR)	Behcet syndrome	Azoospermia and oligospermia found in 13 out of 17 patients treated with CYC. High mean FSH levels in CYC-treated patients	–	–	NR	L CS
Trompeter *et al.* (1981) UK	19 (22) 17 (23)	Nephrotic syndrome	Lower ejaculate volumes and sperm densities and higher percentage of immotile and abnormal forms in CYC exposed group.	–	–	NR	L CS
Marina and Barcelo (1979) Spain	3 (NR) 0	Nephrotic syndrome	All patients showed abnormalities: oligospermia (1), azoospermia (1) and aplasia of germinal epithelium (1).	–	NR	NR	NA Case series
Hsu *et al.* (1979) Canada	16 (NR) 0	Nephrotic syndrome	Sperm quality abnormalities found in 63%. An increase in the total dosage and in duration of the treatment was associated with a higher incidence of testicular dysfunction.	–	–	NR	L Ch
Etteldorf *et al.* (1976) USA	12 (NR) 0	Nephrotic syndrome	Low doses (2–4 mg/kg/day) did not influence pituitary gonadal function (confirmed by biopsy).	–	–	NR	NA Case series
Kirkland *et al.* (1976) USA	15 (NR) 0	Nephrotic syndrome	Serum testosterone levels were normal in CYC-treated patients	NR	*	NR	NA Case series
Pennisi *et al.* (1975) USA	23 (NR) 0	Nephrotic syndrome	Sperm quality was uniformly decreased in CYC-treated patients and high FSH levels were common.	–	–	NR	L Case series
Kumar *et al.* (1972) UK	8 (NR) 0	Nephrotic syndrome	All eight biopsy specimens had evidence of testicular atrophy, and it was profound in 6.	–	NR	NR	L CS

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Penso *et al.* (1974) USA	7 (NR) 0	Nephrotic syndrome	Biopsies confirmed absent spermatogenesis in azoospermic patients and FSH elevation correlated with degree of testicular damage.	–	–	NR	L CS
Feng *et al.* (1972) Singapore	1 (18) 0	Nephrotic syndrome	First case report that reported azoospermia associated with CYC exposure.	–	NR	NR	NA CR
Masala *et al.* (1997) Italy	15 (NR) 0	Nephrotic syndrome	All 15 patients received CYC and became azoospermic or oligospermic. Five patients received testosterone (100 mg intramuscularly every 15 days during CYC therapy). After CYC treatment, normal sperm analysis was reported in all five patients who received testosterone (vs 1/10)	–	NR	NR	L CS
Fairley *et al.* (1972) Australia	31 (31.2) 0	NR	Testicular biopsy was performed on five patients who were receiving CYC and no spermatogenesis was found.	–	NR	NR	L CS
Methotrexate							
Sussman and Leonard (1980) USA	1 (26) 0	Psoriasis	Case report: reversible oligospermia secondary to MTX.	–	NR	NR	NA CR
Van Scott and Reinertson (1959) USA	2 (NR) 0	Psoriasis	Sperm count was reduced to 63–97% at 2 weeks after a single IV injection of MTX.	–	NR	NR	NA Case series
El-Beheiry *et al.* (1979) Egypt	26 (33–52) 0	Psoriasis	The mean difference in sperm count, motility and abnormal forms before and after methotrexate therapy was not significant. Five testicular biopsies performed where no alterations were found.	*	NR	NR	L CS

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Grunnet *et al.* (1977) Denmark	10 (23–46) 0	Psoriasis	Sperm abnormalities found in 40% of MTX-treated patients but sperm quality was better than in patients treated with glucocorticoids.	+	NR	NR	L CS
Ley *et al.* (2018) USA	7 (28) 1912 (NR)	IBD	In all MTX-treated patients, basic semen analyses were within normal limits	−DFI *sperm	NR	NR	L CC
Pandhi *et al.* (2006) India	1 (50)	Psoriasis	Case report: gynaecomastia and oligospermia secondary to MTX	−	NR	NR	NA CR
NSAIDs							
Kristensen *et al.* (2018) Denmark	14 (NR) 17 (NR)	Healthy participants **Ibuprofen**	Experiment: exposure to ibuprofen in adult testis explants caused a state of compensated hypogonadism.	NR	−	NR	NA RCT
Poratsoldin and Soldin (1992) USA	19 (NR) 0	Healthy participants **Salicylate**	*In vitro* study: salicylate significantly decreases sperm motility	−	NR	NR	H CS
Bendvold *et al.* (1985) Sweden	6 (NR) 0	Healthy participants **Naproxen**	Treatment with naproxen significantly reduces the concentration of all PGs present in human seminal fluid.	NR	NR	NR	H CC
Albert *et al.* (2013) France	NA	Healthy participants **Aspirin and indomethacin**	*In vitro* study: production of testosterone by Leydig cells was altered by exposure to all these drugs	NR	−	NR	L CS
Knuth *et al.* (1989) Germany	10 (25.1) 12 (27.4)	Healthy participants **Indomethacin**	Exposure to indomethacin led to lower PGs levels in seminal plasma but unchanged sperm quality parameters and levels of reproductive hormones.	*	*	NR	L CS

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Retinoids							
Liu *et al.* (2017) China	31 (NR) 14 (NR)	Psoriasis Acitretin	After 3 months of treatment at doses of 20 mg/day and 30 mg/day, sperm quality did not differ between cases and controls.	*	*	NR	H CC
Schmitt-Hoffmann (*et al.* 2011) Switzerland	24 (30) 0	Healthy participants Acitretin	After 3 months of treatment at doses of 20 mg or 40 mg/day alitretinoin and 4-oxo-alitretinoin were detected in 11 of 12 semen samples.Concentrations detected are unlikely associated with teratogenicity.	NR	NR	NR	L CC
Rossi and Pellegrino (2009) Italy	1 (39) 0	Psoriasis Acitretin	Case report: 39-year old diagnosed with psoriasis reported erectile dysfunction after starting treatment with acitretin (25 mg/day). After 2 weeks of drug withdrawal, patient reported normalisation of sexual activity.	NR	NR	–	NA CR
Parsch *et al.* (1990) Germany	5 (34) 6 (34)	Psoriasis Acitretin	After 3 months of treatment at doses of 25–50 mg/day, sperm quality did not differ between cases and controls	*	*	NR	H CC
Çinar *et al.* (2016) Turkey	81 (22.6) 0	Acne Isotretinoin	After 6 months of treatment at doses of 120 mg/day, all the sperm quality parameters changed positively and reproductive hormone levels did not differ.	+	*	NR	H CS
Torok *et al.* (1987) Hungary	13 (27) 0	Acne Isotretinoin	After 4 months of treatment at doses of 1 mg/kg/day, sperm motility increased significantly and the other sperm quality parameters did not differ.	+	NR	NR	H CS
Coleman and MacDonald (1994) UK	1 (29) 0	Acne Isotretinoin	Case report of ejaculatory failure associated with isotretinoin (1 mg/kg/day).	NR	NR	–	NA CR

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Healy *et al.* (2018) UK	47 (NR) 0	Acne Isotretinoin	Independent drug safety website (RxISK.org) data: isotretinoin commonly associated with SD.	NR	NR	–	H Ch
Systemic glucocorticoids							
McDonald and Heckel (1956) USA	4 (NR) 7 (NR)	RA	Case series: biopsies performed after exposure to 75 mg of cortisone, and no negative effect was observed.	*	NR	NR	NA Case series
Martens *et al.* (1994) USA	36 (62) 70 (68)	RA	Compared to healthy controls, RA patients taking prednisone had significantly lower testosterone levels and slightly elevated levels of FSH and LH.	NR	–	NR	L CS
Thiopurines (AZA, Azathioprine)							
Dejaco *et al.* (2001) Austria	23 (32) 0 (NR)	IBD **AZA**	Semen analyses of 23 patients with IBD showed no negative association between AZA therapy and sperm quality.	*	NR	NR	L CS
Farthing and Dawson (1983) UK	5 (NR) 0	IBD **AZA**	80% of patients had oligospermia.	–	NR	NR	NA Case series
Baumgarten *et al.* (1977) USA	7 (NR) 0	Kidney transplantation **AZA**	No correlation between poor spermatogenesis and AZA was reported.	*	*	NR	NA Case series
Grosen *et al.* (2019c) Denmark	40 (27.6) 40 (23.3)	IBD **AZA**	Sperm motility was decreased in patients, DFI was similar.	–DFI *sperm	*	NR	H Ch
TNF-α inhibitors (INF, infliximab; ETN, etanercept; CZP, certolizumab pegol; ADA, adalimumab; GOL, golimumab)							
Heppt *et al.* (2017) Germany	27 (37.5) 0	Psoriasis **ETN** **ADA**	Compared with baseline, no significant differences in mean total sperm number, sperm concentration, total and progressive motility nor other semen parameters were noticed during follow-up.	*	NR	NR	L Ch

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
Pascarelli *et al.* (2017) Italy	10 (NR) 0	Healthy participants **ETN**	**In vitro* study: TNF-α had a detrimental effect on sperm function and *in vitro* etanercept counteracted this toxic action of TNF-α.	+	NR	NR	L CS
Ramonda *et al.* (2014) Italy	10 (28.7) 20 (27.4)	SpA **ADA**	Improvement in semen parameters after 12 months of TNF-α inhibitor treatment was reported.	+	*	NR	H CC
Micu *et al.* (2014) Rumania	23 (34.7) 42 (34.8)	AS **ETN (2)** **ADA (14)** **INF(4)**	Exposure of 20 patients to three different types of anti-TNFs did not have a negative impact on sperm quality after 3–6 months and in six cases after 12 months of treatment.	*	NR	NR	L CC
Almeida *et al.* (2013) Brazil	10 (33) 24 (28.5)	AS **ETN (2)** **ADA (8)**	Sperm abnormalities were comparable in patients and controls after 6 months of TNF-α inhibitor therapy.	*	*	NR	H CC
Villiger *et al.* (2010) Switzerland	15 (29.5) 102 (30)	SpA **ETN** **ADA** **INF**	Impaired sperm quality was especially found in the group of anti-TNF naive patients with active disease. Sperm quality tended to improve within the five paired samples for sperm vitality ($P = 0.08$) and sperm motility ($P = 0.08$).	+	*	NR	L CC
Mahadevan *et al.* (2005) USA	10 (31) 0	IBD **INF**	Sperm motility, or the percentage of sperm that show flagellar motion, was below normal in study patients after INF treatment.	−	NR	NR	H CS
Perrier d'Hauterive *et al.* (2012) Belgium	10 (NR) 10 (NR)	Healthy participants **CZP**	CZP treatment was found to have no effect on the semen quality variables assessed vs placebo	*	NR	NR	NA RCT
Grosen *et al.* (2019a) Denmark	28 (30.8) 17 (27.5)	IBD **INF (38)** **ADA(7)**	A statistically significant reduction in DFI was observed after the start of anti-TNF-α therapy (median DFI 12.8 off therapy versus 10.0 on therapy, $P = 0.02$).	*sperm +DFI	NR	NR	H Ch

(continued)

Table I Continued

Reference Country	Number of cases and controls (with mean age in years)	Disease	Key findings	Effect on fertility	Effect on reproductive hormones	Effect on sexual function	NOS quality assessment Study type
			No differences in sperm quality parameters were found between groups.				
Montagna *et al.* (2005) Italy	3 (40) 0	AS **INF**	Case series reporting asthenoazoospermia in two out of three patients using infliximab.	−*	NR	NR	NA Case series
Wildi and Haraoui (2012) Canada	1 (35) 0	AS **ADA**	Case report: oligoasthenozoospermia and decreased motility reversed after stopping drug.	−*	NR	NR	NA CR
Younis *et al.* (2014) Israel	1 (50)	AS **INF**	Case report: low sperm count, concentration increased after stopping IFX.	−*	NR	NR	NA CR
Micu *et al.* (2019) Romania	5 (NR) 0	SpA **ADA**	Normospermia before and after TNF-α therapy initiation.	*	NR	NR	L Ch
Kreitenberg *et al.* (2015) USA	1 (58)	RA **ADA**	Case report: priapism associated with adalimumab.	NR	NR	−	NA CR
Oh *et al.* (2009) Korea	22 (37.8) 0	AS **ETN** **ADA** **INF**	Anti-TNF-α-treated patients showed significant improvements in four out of the five IIEF domains.	NR	NR	+	L Ch
Verdolizumab							
Grosen *et al.* (2019b) Denmark	15 (33) 33 (23)	IBD	Sperm quality and DFI were similar amongst cases and controls after exposure to verdolizumab. Verdolizumab was detected in seminal plasma at levels that correspondent to 0.3–1.1% of serum levels.	*	*	NR	L CC

H, high; L, low; NA, not applicable; NR, not reported; *, no differences reported; +, positive effect; −, negative effect; −*, reversible negative effect upon withdrawal; CC, case–control study; Ch, cohort study; CR, case report; CS, cross-sectional study; RCT, randomised controlled trial.

Table II Summary of study characteristics and main findings for pregnancy and child outcomes.

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
Calcineurin inhibitors (CsP, ciclosporine; SIR, sirolimus; TAC, tacrolimus)								
Hospital Germany Schopf 2017 (Schopf, 2017)	Case report 1 male	3 months prior to conception	Ciclosporine	LB 1	NS	NR	BD 0	L
Hospital Sweden Holmgren 2004 (Holmgren *et al.*, 2004)	Case series NR 3 children	Long term	1 Tacrolimus, 2 Ciclosporine	LB 3	NR	BW 3967	BD 0	L
TC* China Xu 2009 (Xu *et al.*, 2009)	Case series 1981–2007 164 males	Long term	Ciclosporine	LB 167	PB 7	BW 3274 ± 395	BD 1	L
Hospital Turkey Ecevit 2017 (Ecevit *et al.*, 2012)	Case series 1997–2010 2 males	Long term	1 Sirolimus, 1 Tacrolimus	LB 2	PB 0	BW >3500	BD 0	L
TPR* USA Moritz 2017 (Moritz *et al.*, 2017)	Case series 1991-2017 29 pregnancies	Long term	Sirolimus	LB 28 SA 1	NR	NR	BD 1	L
PBR* Denmark Egeberg 2017 (Egeberg *et al.*, 2017)	Cohort 2004–2010 67 / 417567 children	3 months prior to conception and during the first trimester	Ciclosporine/no immunosuppressants	NA	PB 4 (6.0)/18 968 (4.5) OR (95% CI) 1.34 (0.49–3.67) Adj. OR (95% CI) 1.40 (0.51–3.85)	LBW <3/22 087 (5.3) OR (95% CI) 0.55 (0.14–2.25) Adj. OR (95% CI) 0.58 (0.14–2.39)	BD 7 (10.5)/31231 (7.5) OR (95% CI) 1.44 (0.66–3.16) Adj. OR (95% CI) 1.45 (0.66–3.19)	H

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
Colchicine								
Hospital Israel Levy 1977 (Levy and Eliakim 1977)	Case series 3 pregnancies	3 months prior to conception	Colchicine	LB 3	NR	NR	NR	L
Ehrenfeld 1985 (Ehrenfeld *et al.*, 1986)	Case series 11 years 12 (8) children (fathers)	3 months prior to conception	Colchicine	LB 9 SA 3	NR	NR	NR	L
Ben-Chetrit 2004 (Ben-Chetrit *et al.*, 2004)	Cohort 1995–2003 158/64 Pregnancies	3 months prior to conception	Colchicine	SA 10 (6)/6 (9)	NR	NR	NR	L
Cyclophosphamide								
Hospital Turkey Balci 1983 (Balci and Sarikayalar, 1983)	Case report 1 child	Long term	Cyclophosphamide	LB 1	NR	NR	BD 1	L
Interleukin inhibitors								
TIS Germany Weber-Schoendorfer 2016 (Weber-Schoendorfer and Schaefer, 2016)	Case series 2011–2014 2 pregnancies	Long term	Tocilizumab	LB 1 SA 1	NR	NR	BD 0	L

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
MAH SD* Youngstein 2017 (Youngstein *et al.*, 2017)	Case series Until 2012 6 (5) children (fathers) 5 (3) children (fathers)	Long term	Anakinra Canakinumab	NA NA	NR NR	NR NR	BD 0 BD 0	L
MAH SD Warren 2018 (Warren *et al.*, 2018)	Case series Until 2017 54 pregnancies	At the time of conception	Secukinumab	LB 29 (54) SA 4 (7) ET 1 (2) PL 20 (37)	PB 1 (2)	NR	BD 1 (2)	L
Methotrexate								
Hospital USA Perry 1983 (Perry, 1983)	Case report 1 male	6 months prior to conception		LB 1	PT 0	BW 2730	BD 0	NA
Hospital USA Griggs 2006 (Griggs and Schwartz, 2006)	Case report 1 male	6 months prior to conception		LB 1	NR	BW 3500	BD 0	NA
Hospital Italy Lamboglia 2009 (Lamboglia *et al.*, 2009)	Case report 1 male	At the time of conception		LB 1	NR	BW 2800	BD 0	NA
TIS France Beghin 2011 (Beghin *et al.*, 2011)	Case series 1997–2009 42 pregnancies (40 fathers)	3 months prior to conception		LB 36 SA 3 ET 3	GA 39.2 ± 1.1 PB 1	BW 3393 ± 407	BD 0	L

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
JuMBO registry Germany Drenches 2018 (Drenches *et al.*, 2018)	Case series Up to 2018 9 pregnancies	At the time of conception		LB 6 SA 2 ET 1	NR	NR	BD 1	L
PBR* Norway UK 2012 (Engeland *et al.*, 2013)	Cohort 2004–2011 5 singleton pregnancies	3 months prior to conception		SA 0	PB 0	SGA 0	BD 0	L
TIS Germany Weber-Schoendorfer 2014 (Weber-schoendorfer *et al.*, 2014)	Cohort 1995–2012 113/412 pregnancies	3 months prior to conception		LB 87/349 (84.7) SA 15/40 (10.2) ET 11/21 (5.1)	GA 39.1/39 PB 8 (9.2)/54 (15.1)	BW 3380/3330	BD major 1 (1.1)/4 (1.1) minor 4 (4.6)/18 (5.0) genetic 1 (1.1)/2 (0.55) all OR (95% CI) 1.02 (0.4–2.5)	L
PBR Denmark Winter 2017 (Winter *et al.*, 2017) Eck 2017 (Eck *et al.*, 2017) Egeberg 2017 (Egeberg *et al.*, 2017)	Cohort 1997–2013 193/1 013 801 live born children (singleton)	3 months prior to conception	Methotrexate/no methotrexate	NA	PB 13 (6.7)/57 088 (5.6) OR (95% CI) 1.27 (0.63–2.56) Adj. OR (95% CI) 1.38 (0.68–2.81)	SGA 6 (3.1)/34 236 (3.4) OR (95% CI) 0.92 (0.37–2.31) Adj. OR (95% CI) 0.98 (0.39–2.50)	BD 10 (5.2)/48 466 (4.8) OR (95% CI) 1.16 (0.62–2.18) Adj. OR (95% CI) 1.10 (0.57–2.13)	H

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
Andersen 2018 (Andersen *et al.*, 2018) Andersen 2019 (Andersen *et al.*, 2019)	Cohort 1997–2015 520/1 363 543 fathers	3 months prior to conception and during the first trimester	Methotrexate/no methotrexate	SA 46 (8.9)/122 929 (9.0) Adj. HR (95% CI) 0.99 (0.67–1.46)	GA 39.7 (38.7–41.0)/40.0 (39.0–41.0) NA	BW 3510 (3198–3915)/3540 (3200–3890) NA	NA	L
Mycophenolate acid products								
TPR* USA Moritz 2017 (Moritz *et al.*, 2017)	Cohort 1991–2017 295/1092 pregnancies	Long term	MPA/no MPA	LB (90.2)/(91.9) SA (9.2)/(6.2) ET 0/(0.6) SB (0.7)/(0.7) OT 0/(0.6)	GA 39 ± 2.5/39 ± 2.3 PT (12.8)/(12.8)	BW 3323 ± 635/3362 ± 592 LBW (8.5)/(6.6)	BD (3.5)/(3.1)	H
PBR* Norway Midtvedt 2017 (Midtvedt *et al.*, 2017) Åsberg 2017 (Åsberg *et al.*, 2017)	Cohort 1995–2015 155 (112)/195 (133) children (fathers)	Long term	MPA/no MPA	LB 154 (99.4)/191 (97.9) SB 1 (0.6%)/4 (2.1%)	GA 38.8 ± 2.5/39.1 ± 2.7	BW 3381 ± 681/3429 ± 714	BD 6 (3.9)/5 (2.6)	H
PBR* Denmark Egeberg 2017 (Egeberg *et al.*, 2017)	Cohort 2004–2010 6/417 628 children	3 months prior to conception and during the first trimester	Mycophenolate mofetil/no immunosuppressants	NA	PB 0/18 972 (4.5)	LBW 0/22 089 (5.3)	BD 0/31 238 (7.5)	H
Hospital Spain Lopez-Lopez 2018 (Lopez-Lopez *et al.*, 2018)	Cohort 1988–2015 28 (20)/21 (13) children (fathers)	Long term	MPA/no MPA	LB 28/21 SA 6/2		BW 3298 ± 646/3148 ± 401	BD 0/1	L

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
Other selective immunosuppressants								
TIS Italy De Santis 2005 (De Santis *et al.*, 2005)	Case report 1 pregnancy	At the time of conception	Leflunomide	LB 1	GA 38	BW 3350	BD 0	NA
MAH SD* Kumar 2015 (Kumar *et al.*, 2015)	Case series 1995–2014 10 pregnancies	At the time of conception	Abatacept	LB 9 ET 1	NR	NR	BD 0	L
MAH SD Mahadevan 2018 (Mahadevan *et al.*, 2018) Clowse 2016 (Clowse *et al.*, 2016)	Case series Until 2017 84 pregnancies	At the time of conception	Tofacitinib	LB 55 (65.5) SA 7 (8.3) PL 21 (25) ND 1 (1.2)	NR	NR	BD 0	L
Retinoids								
Hospital UK Katugampola 2006 (Katugampola and Finlay, 2006)	Case series 1974–2004 3 (2) children (fathers)	Long term	Etretinate	LB 3	NR	NR	BD 0	L
PBR* Norway Engeland 2012 (Engeland *et al.*, 2013)	Cohort 2004–2011 80 singleton pregnancies	3 months prior to conception	Isotretinoin/NR	NR	PB 7 OR (95% CI) 1.8 (0.81–3.8)	NR	BD 1	L

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Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
PBR* Denmark Nørgaard 2019 (Nørgaard and Andersen, 2019)	Cohort 1996–2016 244 pregnancies 205 children	3 months prior to conception and during first trimester	Acitretin/NR	SA Adj. HR (95% CI) 0.76 (0.38–1.51)	NR	NR	BD	L
Systemic corticosteroids								
Hospital USA Penn 1971 (Penn *et al.*, 1971)	Case series 1962–1970 19 males 23 pregnancies	Long term	Prednisone	LB 19 SA 1 PL 3	NR	NR	BD 1	L
Hospital UK McGeown 1978 (McGeown and Nevin 1978)	Case series 8 males	Long term	Prednisolone	LB 11	GA 40.5 PB 0	BW 3741	BD 1	L
TC* China Xu 2009 (Xu *et al.*, 2009)	Case series 1981–2007 164 males	Long term	Prednisone	LB 167	PB 7	BW 3274 ± 395	BD 1	L
PBR* Norway Engeland 2012 (Engeland *et al.*, 2013)	Cohort 2004–2011 1477 singleton pregnancies	3 months prior to conception	Prednisolone	SA 4 OR (95% CI) 0.99 (0.37–2.6)	PB 93 OR (95% CI) 1.0 (0.84–1.3)	SGA 163 OR (95% CI) 1.1 (0.53–2.1)	Any BD 75 OR (95% CI) 0.99 (0.71–1.4) Serious BD 35 OR (95% CI) 0.99 (0.71–1.4)	L

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
PBR* Denmark Larsen 2017 (Larsen *et al.*, 2018)	Cohort 1997–2013 2380 (1558:1 822:2)/1 011 614 live born children (singletons)	3 months prior to conception	Filled prescriptions for systemic corticosteroids 81% prednisone, 12% prednisolone/no filled prescriptions for systemic corticosteroids in 1 year prior to conception	NA	PB 1 presc. 92 (5.91)/56 677 (5.63) OR (95% CI) 1.02 (0.79–1.33) Adj. OR (95% CI) 1.05 (0.80–1.37) PB ≥2 presc. 40 (4.87) 56 677 (5.63) OR (95% CI) 0.81 (0.55–1.19) Adj. OR (95% CI) 0.81 (0.55–1.21)	SGA 1 presc. 56 (3.61)/33 987 (3.39) OR (95% CI) 1.11 (0.82–1.50) Adj. OR (95% CI) 1.13 (0.83–1.56) SGA ≥2 presc. 30 (3.66)/33987 (3.39) OR (95% CI) 1.06 (0.70–1.61) Adj. OR (95% CI) 1.06 (0.68–1.64)	BD 1 presc. 83 (5.33)/50170 (4.98) OR (95% CI) 1.08 (0.86–1.35) Adj. OR (95% CI) 1.08 (0.86–1.36) BD ≥2 presc. 51 (6.20)/50 170 (4.98) OR (95% CI) 1.28 (0.95–1.72) Adj. OR (95% CI) 1.33 (0.99–1.79)	H
Thiopurines (AZA, azathioprine; 6MP, 6-mercaptopurine)								
Hospital USA Penn 1971 (Penn *et al.*, 1971)	Case series 1962–1970 19 males 23 pregnancies	Long term	Azathioprine	LB 19 SA 1 PL 3	NR	NR	BD 1	L
Hospital Israel Ben-Neriah 2001 (Ben-Neriah and Ackerman, 2001)	Case report 1 male	Long term	Azathioprine or 6-mercaptopurine	LB 1	NR	NR	BD 1	NA
Hospital UK McGeown 1978 (McGeown and Nevin 1978)	Case series NR 8 males (13 pregnancies)	Long term	Azathioprine	LB 11 SA 1 SB 1	GA 40.5 PB 0	BW 3741	BD 1	L

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
TC* China Xu 2009 (Xu *et al.*, 2009)	Case series 1981–2007 164 males	Long term	Azathioprine	LB 167	PB 7	BW 3274 ± 395	BD 1	L
Hospital USA Rajapakse 2000 (Rajapakse *et al.*, 2000)	Cohort 1970–1997 13/90 pregnancies	3 months prior to conception and during the first trimester	6-Mercaptopurine/ never taken 6MP or only after conception	SA 2 (15)/2 (2.2)	NR	NR	BD 2 (15)/0	L
Hospital Spain Teruel 2003 (Teruel *et al.*, 2010)	Cohort 2007–2008 46/84 pregnancies	3 months prior to conception	37 Azathioprine or 9-mercaptopurine/no exposure to thiopurines in 3 months prior to conception	SA 5/7 OT 0/4	GA 38.9/39.4 PB 2 (4.3)/2 (2.4)	BW 3063 ± 533/3248 ± 493 LBW 3 (6.5)/5 (6.0)	BD 1 (2.2)/2 (2.4)	H
Hospital USA Francella 2003 (Francella *et al.*, 2003)	Cohort 1950–1997 37/73 pregnancies	At the time of conception	6-Mercaptopurine/ pregnancies prior to treatment 6 MP	LB 30/62 SA 6/11 ET 1/0	PB 3/3	LBW 2/3	BD 1/2	L
TIS* Germany Hoeltzenbein 2012 (Hoeltzenbein *et al.*, 2012)	Cohort 1988–2010 115/340 pregnancies	101 until conception or longer, others not specified	108 Azathioprine, seven 6-mercaptopurine/pregnancies not exposed to teratogens and no paternal reported immunosuppressivedrugs or otherwise risky treatment	LB 100/319 SA 9/24 ET 7/3 SB 0/1	GA 40/40 PB 7 (7)/32 (10)	BW 3520/3400	BD major 3/7 minor 8/13 genetic 0/5	L

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
PBR* Denmark Norgard 2017 (Nørgård *et al.*, 2017) Egeberg 2017 (Egeberg *et al.*, 2017)	Cohort 1997–2013 699//1 012 624 live born children (singletons)	3 months prior to conception	At least one filled prescription of AZA or 6MP within 3 months before the date of conception/no filled prescription of AZA or 6MP within 3 months before the date of conception	NA	PB 35 (5.01)/49 966 (4.93) OR (95% CI) 0.94 (0.61–1.43) Adj. OR (95% CI) 1.17 (0.72–1.92)	SGA 23 (3.31)/29 803 (2.93) OR (95% CI) 1.18 (0.72–1.91) Adj. OR (95% CI) 1.38 (0.76–2.51)	BD 32 (4.58)/48 456 (4.79) OR (95% CI) 0.95 (0.66–1.38) Adj. OR (95% CI) 0.82 (0.53–1.28)	H
TNF-α inhibitors (INF, infliximab; ETN, etanercept; CZP, certolizumab pegol; ADA, adalimumab; GOL, golalinumab)								
Hospital Italy Lamboglia 2009 (Lamboglia *et al.*, 2009)	Case report 1 male	At the time of conception	Infliximab	LB 1	NR	BW 2800	BD 0	NA
Hospital Greece Paschou 2009 (Paschou *et al.*, 2009) Saougou 2013 (Saougou *et al.*, 2013)	Case series 2001–2007 4 males (6 children) 2001–2010 11 males (14 children)	Long term	Infliximab	LB 6 LB 14 ET 1+	NR NR	NR NR	BD 0 BD 0	L L
Hospital Turkey Uyaroglu 2017 (Uyaroglu *et al.*, 2017)	Case series 2015–2016 42 males	At the time of conception	TNF-α inhibitor	LB 38 SA 3 ET 1	GA 39 PB 4 (10.5)	BW 3229 ± 582 LBW 4	BD 0	L

(continued)

Table II Continued

Data source Country Author Year of publication	Type of study Study period Number of cases Number of controls Unit cases	Exposure period	Inclusion Cases Controls	Pregnancy outcome Live births (LB) Spontaneous abortions (SA) ETOP* (ET) Stillbirths (SB) Pending/LTFU* (PL) Neonatal death (ND) Other (OT) n (%)	Gestational age (GA in weeks, mean ± SD) Preterm birth (PB, n (%))	Birth weight (BW in gram, mean ± SD) Low birth weight (LBW, n (%)) Small for gestational age (SGA, n (%))	Birth defects (BD, n (%))	Quality assessment
Hospital Italy Hoxha 2017 (Hoxha *et al.*, 2017)	Case series 2008–2015 3 males	NR	Etanercept	LB 3	NR	NR	BD 0	L
TREAT registry USA Lichtenstein 2018 (Lichtenstein *et al.*, 2018)	Case series 1999–2012 42 pregnancies	At the time of conception	Infliximab	LB 41 (97.6) SA 1 (2.4)	PB 1	NR	BD 1 (2.4)	L
MAH SD* Clowse 2015 (Clowse *et al.*, 2015)	Case series up to 2014 46 pregnancies	At the time of conception	Certolizumab Pegol	LB 27 SA 4 ET 1 SB 1 PL 13	NS	NS	NS	L
PBR Denmark Larsen 2016 (Larsen *et al.*, 2016)	Cohort 2007–2013 372/399 498 live born children (singletons)	3 months prior to conception	TNF-α I:155 Infliximab, 136 Adalimumab, 69 Etanercept, 11 Golimumab*, 1 Certolizumab pegol	NA	PB 21 (5.65)/21 745 (5.44) OR (95% CI) (0.57–1.75) Adj. OR (95% CI) 0.97 (0.54–1.76)	SGA 16 (4.32)/11 871 (2.98) OR (95% CI) 1.51 (0.84–2.71) Adj. OR (95% CI) 1.70 (0.94–31.09)	BD 21 (5.65)/23 244 (5.82) OR (95% CI) 0.97 (0.62–1.54) Adj. OR (95% CI) 0.92 (0.57–1.48)	H
Hospital Romania Micu 2019 (Micu *et al.*, 2019)	Cohort 2012–2017 33/12 142 pregnancies	Long term	TNF-α I/general population data	LB 30 (91)/9667 (79.6) SA 0/1135 (9.4) ET 3 (9.0)/1233 (10.2) SB 0/107 (0.9)	GA 37.57 ± 1.01/NS PB 6 (20.0)/1074 (11.1)	BW 3390 ± 343/NS SGA 0/101 (1.0)	BD 0/140 (1.4)	L

H, high; L, low; NA, not applicable; NR, not reported; PBR, population-based registry; presc., prescriptions; TC, transplantation centre; TIS, Teratology Information Service.

publications included maternal and paternal outcomes, the score was based only on the paternal outcomes.

Synthesis of results

Sexual health outcomes were classified into two categories: (i) sexual function, reproductive hormones and fertility (e.g. sexual dysfunction, testosterone and sperm quality) and (ii) pregnancy and offspring outcomes (e.g. live births, spontaneous abortions, premature birth, low birth weight and congenital anomalies).

Additional analysis

A meta-analysis was not possible to perform due to the heterogenicity of the data.

Results

Study selection and characteristics

A total of 5867 references were identified (2366 from Embase, 2023 from Medline, 1315 from Web of Science and 163 from Cochrane central) and imported into EndNote X9. After removing 1663 duplicates, 4204 articles were eligible for title and abstract screening. During this phase, 3850 articles were excluded and 354 articles were eligible for full-text reading. Then 193 articles were excluded after full-text reading (see flowchart in Fig. 1). Additionally 15 articles that fulfilled the inclusion criteria and that were not identified by our search strategy or that were missed during the screening titles and abstracts procedure were identified by cross-checking relevant literature. In total, 176 articles fulfilled the inclusion criteria.

Description of participants

A brief description of participants' characteristics is provided throughout the text and/or in the tables.

Description of interventions

In general, sexual function and fertility outcomes were evaluated in a few studies before and after exposure to immunosuppressive drugs. In cross-sectional studies, disease activity and co-medication used during the study were not uniformly reported.

The publications regarding pregnancy and child outcomes were observational; no standardised interventions were studied.

Risk of bias within studies

Regarding sexual function, reproductive hormones and male fertility, the overall quality of the included studies was low to moderate and the number of exposed cases was low for all the drugs included in this systematic review. Regarding pregnancy outcomes, case series and small cohorts were of low quality (<5) in general. High scores (≥5) were given to the population-based registries from Denmark and Norway and transplantation registries.

Outcomes

In the upcoming text, we provide a summary of the main outcomes from the included studies. More in-depth information regarding the findings and study quality per study is presented in Tables I and II and in the Supplementary tables. Table I contains information regarding fertility, reproductive hormones and sexual function outcomes. Table II contains information about pregnancy outcomes, gestational age, birth weight and birth defects. Supplementary Table S2 contains more study specifications. Reported specification of the birth defects is presented in Supplementary Table S3. Other maternal and child outcomes are reported in Supplementary Table S4.

Paternal exposure was included in this systematic review if paternal exposure occurred 6 months before conception or around the time of conception. Some of the included studies also presented results for exposure at any time before conception. Comparison between 'exposure 3 months prior to conception' and 'exposure at any time before conception' was possible in publications of the Danish registry data (Larsen *et al.*, 2016; Egeberg *et al.*, 2017; Nørgaard and Andersen, 2019). See Supplementary Table S5 for outcomes after exposures any time before conception. No major changes were found in the risk estimates, only small changes were seen with a very low number of cases.

Aminosalicylic acid and similar agents

Sexual function, reproductive hormones and fertility.

There were 22 studies with data on a total of 329 exposed men to sulfasalazine identified. Sperm analysis abnormalities were reported in 40–100% of those patients exposed to sulfasalazine (doses ranged from 2 to 4 mg/day). The most common sperm abnormality reported was asthenozoospermia (decreased motility) followed by decreased sperm counts and abnormal morphology. Data extracted from case reports and small case series showed that oligospermia and asthenozoospermia were severe enough to cause male infertility. In all studies where follow-up samples were available, sperm quality improved after sulfasalazine was withdrawn for 3 months. The majority of these studies were published between 1979 and 1987 and included patients diagnosed with IBD (Levi *et al.*, 1979; Toth, 1979; Traub *et al.*, 1979; Birnie *et al.*, 1981; Heineman *et al.*, 1981; Toovey *et al.*, 1981; Freeman *et al.*, 1982; Hudson *et al.*, 1982; Tobias *et al.*, 1982; Cann and Holdsworth, 1984; Cosentino *et al.*, 1984; Freixa *et al.*, 1984; McIntyre and Lennard-Jones, 1984; O'Morain *et al.*, 1984; Ragni *et al.*, 1984; Shaffer *et al.*, 1984; Iglesias-cortit *et al.*, 1985; Riley *et al.*, 1987; Chatzinoff *et al.*, 1988; Zelissen *et al.*, 1988; Di Paolo *et al.*, 2001; Ganatra *et al.*, 2018). Importantly, most of these studies are case reports and case series.

Pregnancy and child outcomes.

No studies were identified.

Antimalarials (chloroquine and hydroxychloroquine)

Sexual function, reproductive hormones and fertility.

Four studies that included data from 37 healthy men were identified. One study reported sperm quality parameters and three studies evaluated the ability of chloroquine to cross the blood-testis barrier (Ette *et al.*, 1988; Adeeko and Dada, 1994; Hargreaves *et al.*, 1998; Ejebe

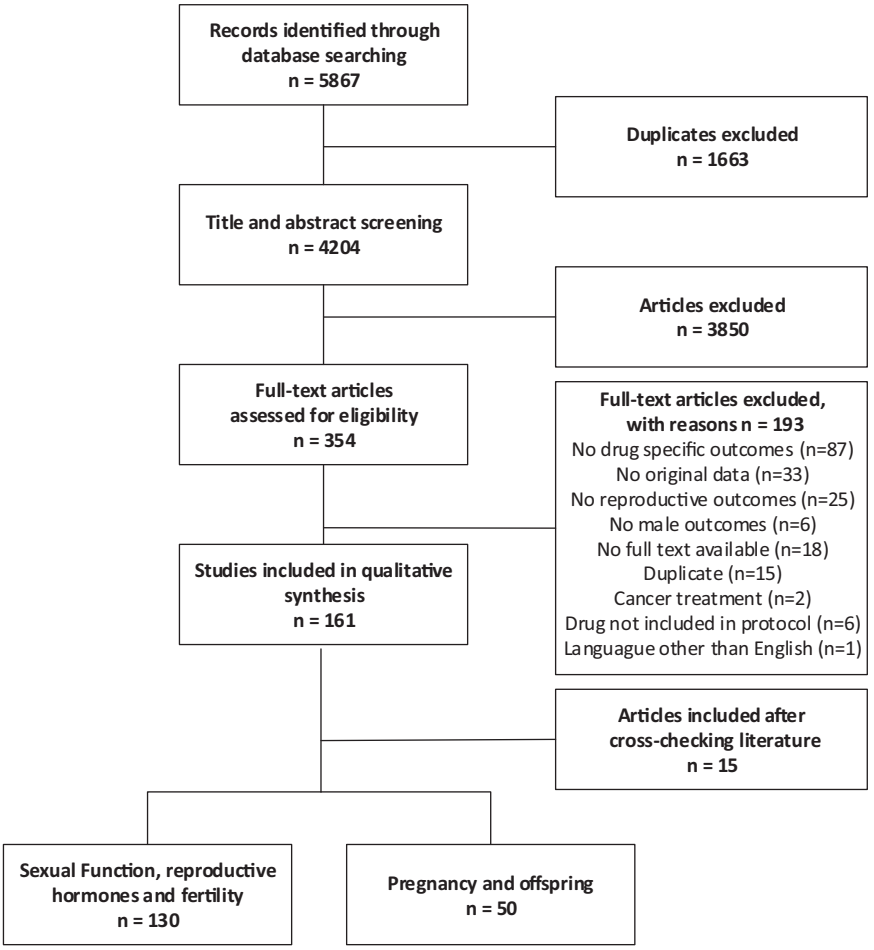

Figure 1. Flow diagram for study selection.

et al., 2008). As it is the case for other human tissues and fluids, chloroquine can be found on seminal plasma even after long-term withdrawal. One *in vitro* study reported that high concentrations of chloroquine in seminal plasma inhibited sperm motility. No studies reporting these outcomes were identified for hydroxychloroquine.

Pregnancy and child outcomes.

No studies were identified.

Calcineurin inhibitors (ciclosporine, sirolimus and tacrolimus)

Sexual function, reproductive hormones and fertility.

Fifteen studies including a total of 263 cases and 229 controls were identified. All of these cases were receiving sirolimus or ciclosporine for organ transplantation (mainly kidney transplantation). In all 11 studies included, sperm quality abnormalities and reproductive hormonal alterations (low testosterone and high FSH/LH levels) were reported after sirolimus exposure (Misro *et al.*, 1999; Bererhi *et al.*, 2003; Fritsche *et al.*, 2004; Kaczmarek *et al.*, 2004; Lee *et al.*, 2005; Tondolo *et al.*, 2005; Deutsch *et al.*, 2007; Skrzypek and Krause, 2007; Zuber *et al.*, 2008; Boobes *et al.*, 2010; Sajad Hussain *et al.*, 2015). In addition, reversible infertility associated with sirolimus was reported in three studies. One prospective study reported that testosterone levels increased from baseline levels (pre-transplant) in an undefined number of patients using everolimus (Kramer *et al.*, 2005). Despite the lack of reproductive safety information for tacrolimus in humans, in these studies, patients were switched from sirolimus to tacrolimus and their sperm quality improved.

Nine post-kidney transplant patients exposed to ciclosporine provided semen samples and no relevant sperm quality abnormalities were reported. From this group of patients, partners of three out of four patients were able to conceive while being exposed to ciclosporine (Haberman *et al.*, 1991; Misro *et al.*, 1999). A prospective study that included pre- and post-kidney transplantation data of 10 men, reported that hypogonadism was present before initiating treatment with ciclosporine. After 12 months of ciclosporine exposure, levels of testosterone exceeded pre-transplant levels (Samojlik *et al.*, 1992). Sexual hormone levels were normal and comparable amongst 21 ciclosporine- and 16 tacrolimus-exposed renal transplant male patients (Kantarci *et al.*, 2004). Similar results were reported by others (Peces *et al.*, 1994). Sperm concentration was

inversely correlated to the ciclosporine whole blood levels in one study (Eid *et al.*, 1996).

Pregnancy and child outcomes.

Six studies were aimed at determining the impact of the use of ciclosporine, tacrolimus or sirolimus on pregnancy and child-related outcomes. Transplant recipients used these medications often in combinations with other drugs.

Three case reports/case series and two transplantation registries found no abnormal outcomes (Moskovitz *et al.*, 1988; Holmgren *et al.*, 2004; Xu *et al.*, 2009; Ecevit *et al.*, 2012; Moritz *et al.*, 2017; Schopf, 2017). A population-based registry found a higher risk of birth defects although this was not statistically significant (Egeberg *et al.*, 2017). Seven of the 67 children were diagnosed with a congenital anomaly (CA) after paternal use of ciclosporine. No details of the CAs were provided.

Colchicine

Sexual function, reproductive hormones and fertility.

Eight studies including a total of 166 cases were identified. Most of these studies were published before 2000. Colchicine exposure (1–2 mg/day) was associated with low sperm counts and motility in five studies (Merlin, 1972; Ben-Chetrit *et al.*, 1993; Sarica *et al.*, 1995; Kirchin *et al.*, 1999; Kaya Aksoy *et al.*, 2019). Abnormal sperm analysis was reported in 40–58% of patients exposed to colchicine (Sarica *et al.*, 1995; Kaya Aksoy *et al.*, 2019). One study reported normal cytogenic sperm analysis in two patients diagnosed with gout and exposed to colchicine (Kastrop *et al.*, 1999), one study reported no significant sperm analysis abnormalities in patients previously exposed to colchicine (Levy and Eliakim, 1977) and finally, one study reported no significant sperm abnormalities in healthy volunteers exposed to colchicine (Bremner and Paulsen, 1976). A possible adverse effect on sperm quality associated with disease activity was discussed in the most recent study by Kaya Aksoy *et al.* (2019).

Pregnancy and child outcomes.

Three older studies from an Israeli hospital followed patients with familial Mediterranean fever (FMF) treated with colchicine (Levy and Eliakim, 1977; Ehrenfeld *et al.*, 1986; Ben-Chetrit *et al.*, 2004). Only one study reported specific data on colchicine and spontaneous abortions (no increased risk) (Ben-Chetrit *et al.*, 2004); the other studies did not report specific outcomes for colchicine-treated patients.

Cyclophosphamide

Sexual function, reproductive hormones and fertility.

There were 20 studies identified, and most of them included patients who were exposed to cyclophosphamide (CYC) to treat nephrotic syndromes associated with glomerulonephritis (73%). Most of these studies reported fertility outcomes from young adults who were exposed to CYC during their childhood. Unfortunately, the mean age of these participants was not reported in many studies. From these studies, a clear negative effect on sperm quality and reproductive hormones, mainly causing low sperm counts and high FSH levels, from CYC is evident (Fairley *et al.*, 1972; Feng *et al.*, 1972; Kumar *et al.*, 1972; Penso *et al.*, 1974; Pennisi *et al.*, 1975; Etteldorf *et al.*, 1976; Kirkland *et al.*, 1976; Hsu *et al.*, 1979; Marina and Barcelo, 1979; Fukutani *et al.*, 1981; Trompeter *et al.*, 1981; Ogata *et al.*, 1982; Watson *et al.*, 1985; Perrone *et al.*, 1989; Bogdanovic *et al.*, 1990; Masala *et al.*, 1997; Anserini *et al.*, 2002; Soares *et al.*, 2007; Suehiro *et al.*, 2008). Reversibility (improvement in sperm counts after CYC withdrawal) with a possible dose-dependent effect was a repetitive finding in some studies. Because of substantial methodological problems (selection bias, loss of follow-up and no baseline samples), reversibility and a dose-dependent effect cannot be interpreted as conclusive evidence.

Pregnancy and child outcomes.

In 1983, a case report was published noting that a child was born with an absent hand after paternal exposure to cyclophosphamide and dexamethasone (Balci and Sarikayalar, 1983).

Interleukin inhibitors

Sexual function, reproductive hormones and fertility.

No studies were identified.

Pregnancy and child outcomes.

Three case series from different sources focused mainly on maternal exposures and briefly mentioned paternal exposures (Weber-Schoendorfer and Schaefer, 2016; Youngstein *et al.*, 2017; Warren *et al.*, 2018). The paternal exposures included two pregnancies where the male partners were on tocilizumab (one healthy liveborn and one spontaneous abortion), and 54 pregnancies on where the male partners were on secukinumab (Weber-Schoendorfer and Schaefer, 2016). Outcomes were not available for 20 pregnancies (7 were pending and 13 were lost to follow-up), while known outcomes were 29 liveborn with one malformation, four spontaneous abortions and one elective termination (Warren *et al.*, 2018).

Youngstein *et al.* reported six children with paternal exposure of anakinra and five children with paternal exposure of canakinumab; no malformations were reported (Youngstein *et al.*, 2017).

Methotrexate

Sexual function, reproductive hormones and fertility.

Six studies reporting fertility outcomes in patients exposed to methotrexate (MTX) were identified. These studies included a total of 47 cases (40 men diagnosed with psoriasis and seven with IMD) and 1912 controls (all controls come from one study (Ley *et al.*, 2018)). In patients exposed to MTX, sperm concentration decreased in three studies (Van Scott and Reinertson, 1959; Sussman and Leonard, 1980; Pandhi *et al.*, 2006), no differences were reported in two studies (one study reported five normal testicular biopsies after MTX exposure) (El-Beheiry *et al.*, 1979; Ley *et al.*, 2018) and the sperm quality of one group of patients diagnosed with psoriasis and exposed to MTX was better than patients treated with high dose glucocorticoids (Grunnet *et al.*, 1977).

Pregnancy and child outcomes.

Three case reports from before 2000 reported only healthy liveborn children (Perry, 1983; Griggs and Schwartz, 2006; Lamboglia *et al.*, 2009). More recent case series and cohort studies (169 pregnancies and 193 liveborn children) found no increased risk of birth defects associated with paternal MTX exposure (Beghin *et al.*, 2011; Engeland *et al.*, 2013; Weber-schoendorfer *et al.*, 2014; Winter *et al.*, 2017;

Drenches et al., 2018). This also applies to the rate of spontaneous abortions, preterm birth and small for gestational age (SGA; Weber-schoendorfer et al., 2014; Winter et al., 2017; Andersen et al., 2018).

Friedman et al. used the Danish registries to look at long-term outcomes and no negative impact of paternal preconception use of MTX was reported (Friedman et al., 2017).

Mycophenolate acid products

Sexual function, reproductive hormones and fertility.

No studies were identified.

Pregnancy and child outcomes.

Four data sources have published data with 295 pregnancies and 189 children included: three registries, two population-based and one pregnancy transplantation with medical records from one hospital in Spain (Jones et al., 2013; Åsberg et al., 2017; Egeberg et al., 2017; Midtvedt et al., 2017; Moritz et al., 2017; Lopez-Lopez et al., 2018). No major differences were found compared to transplantation patients not taking mycophenolate acid products (MPAs). In these studies, MPA was often used in combination with calcineurin inhibitors and corticosteroids.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Sexual function, reproductive hormones and fertility.

For NSAIDs as a group, no studies were identified in our population of interest. Nonetheless, six studies that included healthy participants were identified. Exposure to salicylate decreased sperm motility, and for naproxen one study concluded that sperm quality abnormalities were similar between pre- and post- exposed samples (Bendvold et al., 1985; Knuth et al., 1989; Poratsoldin and Soldin, 1992). A study from Kristensen et al. concluded that ibuprofen exposure results in a state of compensated hypogonadism (Kristensen et al., 2018). One *in vitro* study using adult human testis explants demonstrated that exposure to indomethacin and aspirin altered the production of testosterone by Leydig cells (Albert et al., 2013).

Pregnancy and child outcomes.

No studies were identified.

Retinoids (acitretin, etretinate and isotretinoin)

Sexual function, reproductive hormones and fertility.

Eight studies that included a total of 203 cases and 20 controls were identified (Torok et al., 1987; Parsch et al., 1990; Coleman and MacDonald, 1994; Rossi and Pellegrino, 2009; Schmitt-Hoffmann et al., 2011; Çinar et al., 2016; Liu et al., 2017; Healy et al., 2018). Low concentrations of retinoids that are unlikely associated with a teratogenic risk can be found in seminal plasma of exposed patients (Schmitt-Hoffmann et al., 2011). No negative effect on sperm quality was reported in four studies (130 exposed men). Sexual dysfunction in the form of ejaculatory failure and erectile dysfunction associated with acitretin has been reported (Healy et al., 2018).

Pregnancy and child outcomes.

Three studies report paternal retinoid use and pregnancy-related outcomes. Two included only liveborn children. A long-term general follow-up study after etretinate use, with 18 male patients, found three healthy children (Katugampola and Finlay, 2006). Population-based registries from Norway found a higher risk (OR (95% CI) 1.8 (0.81–3.8) for preterm birth (live birth after at least 22 and prior to 37 weeks of gestation) based on 80 isotretinoin cases (Engeland et al., 2013). Based on population-based registries, a study from Denmark found no risk for spontaneous abortion after acitretin use (Nørgaard and Andersen, 2019).

Systemic corticosteroids

Sexual function, reproductive hormones and fertility.

Two studies were identified. In a study from 1956, seven patients diagnosed with RA were treated with 75 mg of cortisone over periods ranging from 23 to 334 days. Pre- and post-treatment testicular biopsies were performed for six patients, in which no significant changes were reported (McDonald and Heckel, 1956). In a small study that included 36 men with long standing active RA, the use of prednisone at doses ranging from 5 to 10 mg/day was associated with significantly lower testosterone levels and lower levels of FSH and LH compared to men with long standing RA but without prednisone treatment (Martens et al., 1994). Because of the scope of our systematic review, studies that reported the effect of corticosteroids on the male reproductive health of healthy controls were excluded. A review on this topic can be found elsewhere (Drobnis and Nangia, 2017).

Pregnancy and child outcomes.

A high number of cases were reported in the population-based studies of Norway and Denmark. Data from Norway refer to prednisolone (Engeland et al., 2013). No drug-specific information about systemic corticosteroids in the Danish data was available and both registries have no information about the used dose or indication. Larsen et al. only found a higher risk of birth defects in the Danish registries, although it was not statistically significant, after one or two redeemed prescriptions (Larsen et al., 2018). Smaller numbers are reported in transplantation patients (Penn et al., 1971; McGeown and Nevin, 1978; Xu et al., 2011).

Thiopurines

Sexual function, reproductive hormones and fertility.

Four studies that included a total of 75 cases and 40 controls exposed to azathioprine were included (Baumgarten et al., 1977; Farthing and Dawson, 1983; Dejaco et al., 2001; Grosen et al., 2019c). Sperm quality, sperm DNA fragmentation index (DFI) and the male endocrine reproductive axis appear not to be negatively affected by azathioprine exposure.

Pregnancy and child outcomes.

Azathioprine is the most frequently reported thiopurine followed by 6-mercaptopurine. The first hospital case series were reported in the 1970s (Penn et al., 1971; McGeown and Nevin, 1978). In the early 2000s, other case series followed and the largest study up to now was based on the Danish registries from 2017. No differentiation between the two drugs was made (Rajapakse et al., 2000; Francella et al., 2003;

Xu *et al.*, 2009, 2011; Teruel *et al.*, 2010; Hoeltzenbein *et al.*, 2012; Nørgård *et al.*, 2017). In total 192 males, 211 pregnancies and 669 children were included in these studies. Overall, no increased risks were detected.

Friedman *et al.* used the Danish registries to look at long-term outcomes and no negative impact of paternal preconception use of azathioprine or 6-mercaptopurine was reported (Friedman *et al.*, 2017).

Tumour necrosis factor-α inhibitors

Sexual function, reproductive hormones and fertility.

We identified 15 studies that evaluated the effect of tumour necrosis factor (TNF)-α inhibitors on male sexual health. Thirteen studies reported fertility or sperm quality outcomes, one study reported sexual function as an outcome (Oh *et al.*, 2009) and priapism secondary to the use of adalimumab was reported in one case report (Kreitenberg *et al.*, 2015). In total, outcomes of interest were reported in 156 men diagnosed with ankylosing spondylitis (AS), psoriasis, RA and IBD exposed to TNF-α inhibitors and in 225 men who participated in these studies as healthy controls.

Regarding sperm quality before and after TNF-α inhibitor use, one small randomised control trial (RCT) that included data of 20 men concluded that certolizumab pegol had no adverse event on sperm quality compared to placebo (Perrier d'Hauterive *et al.*, 2012). In studies where a comparison between baseline samples before TNF-α inhibitor exposure and follow-up samples was available, no differences on sperm quality were reported in five studies (Almeida *et al.*, 2013; Micu *et al.*, 2014, 2019; Heppt *et al.*, 2017; Grosen *et al.*, 2019a), while in three studies sperm quality improved after exposure (Villiger *et al.*, 2010; Ramonda *et al.*, 2014; Pascarelli *et al.*, 2017) and in one study sperm quality worsened after exposure (Mahadevan *et al.*, 2005). A possible positive effect on sperm quality using TNF-α inhibitors could be the result of decreasing disease activity in patients with AS. These findings should not be extrapolated to other diseases until more research is available.

One study showed that exposure to TNF-α inhibitors in a group of men diagnosed with AS resulted in improvement of sexual function scores (Oh *et al.*, 2009).

Pregnancy and child outcomes.

Eight small studies and one large population-based cohort were identified (Lamboglia *et al.*, 2009; Paschou *et al.*, 2009; Saougou *et al.*, 2013; Clowse *et al.*, 2015; Larsen *et al.*, 2016; Hoxha *et al.*, 2017; Uyaroglu *et al.*, 2017; Lichtenstein *et al.*, 2018; Micu *et al.*, 2019). In total, 61 males, 121 pregnancies and 372 children were included. Overall, no increased risk was found. Larsen found a higher risk for SGA infants based on 16 cases, although this was not statistically significant.

Verdolizumab

Sexual function, reproductive hormones and fertility.

One study from Denmark that included data on 15 male patients diagnosed with IBD with a mean age of 33 years and 40 healthy controls with a mean age of 23 years was identified. After exposure to verdolizumab, the sperm DFI was similar amongst the two groups (Grosen *et al.*, 2019b).

Pregnancy and child outcomes.

No studies were identified.

Other selective immunosuppressants

Pregnancy and child outcomes.

All publications contained mostly maternal exposure cases and only briefly mention paternal exposures. The results for the paternal exposure were one case report on leflunomide reporting a healthy child (De Santis *et al.*, 2005) and two case series from the industry on abatacept (10 pregnancies) and tofacitinib (84 pregnancies) revealing no safety concerns (Kumar *et al.*, 2015; Mahadevan *et al.*, 2018).

Immunosuppressive drugs without available information

For many immunosuppressive drugs, no studies were identified. In Table III, the most relevant immunosuppressive drugs where no available data were available are presented.

Treatment of antisperm antibodies

Antisperm antibodies are considered as an important cause of male infertility and often are associated with autoimmunity. Although not included in the original scope of our systematic review, we identified a considerable number of studies regarding the treatment of antisperm antibodies (mainly associated with male infertility) using glucocorticoids. These studies reported mixed results and overall the risks associated with glucocorticoid therapy outweighed the benefits. In-depth information can be found elsewhere (Drobnis and Nangia, 2017).

Discussion

Summary of evidence

Sexual function, reproductive hormones and fertility.

Regarding sexual function, reproductive hormones and fertility, most of the available information focuses on the effect of immunosuppressive drugs on male fertility (specifically on sperm quality). Less information was available for sexual function or reproductive hormones.

Based on the available information on the effect of immunosuppressive drugs on male sexual function, reproductive hormones and fertility, the following classification is provided.

No negative effect was observed for acitretin, azathioprine, ciclosporine, isotretinoin, TNF-α inhibitors and verdolizumab.

Negative effects were reported for cyclophosphamide, sirolimus and sulfasalazine.

Unclear effects were noted for chloroquine, colchicine, methotrexate, NSAIDs and systemic glucocorticoids.

Worth mentioning is that TNF-α plays an important role in spermatogenesis and testicular homeostasis; one of the main findings for this group of drugs is that disease activity itself might play a role in baseline sperm quality characteristics and on the subsequent effect that TNF-α inhibitors have on sperm quality. At least for patients diagnosed with AS, TNF-α inhibitors appeared to have a positive effect on sperm quality. As it is the case for most of the drugs included in this systematic review, further research is needed.

Table III Immunosuppressive drugs included in the search strategy without studies included in the final data analysis.

Sexual function, reproductive hormones and fertility		Pregnancy outcomes	
Anakinra	JAK inhibitors	Apremilast	JAK inhibitors
Apremilast	Leflunomide	Belimumab	NSAIDs
Belimumab	Rituximab	Canakinumab	Rituximab
Canakinumab	Ruxolitinib	COX 2 inhibitors	Ruxolitinib
Human immunoglobulin	Secukinumab	Everolimus	Sulfasalazine
Hydroxychloroquine	Tacrolimus	Human immunoglobulin	Tioguanine
Ixekizumab	Tocilizumab	Ixekizumab	Tocilizumab

Disease activity was taken into consideration in the study design of a few studies. By doing this, authors showed that disease activity can also induce sperm abnormalities (Villiger *et al.*, 2010; Ganatra *et al.*, 2018; Kaya Aksoy *et al.*, 2019). Considering that IMDs have different inflammatory phenotypes, the effect of disease activity could be an important confounder in future studies on the impact of medications on sperm quality.

Pregnancy and child outcomes.

Regarding pregnancy and child outcomes, we found no clear evidence to support restriction in the prescription of these drugs. Although the number of patients was low in case reports and series, and in small cohorts, in some cases, detailed information is available. In contrast, in population-based registries, predominantly from Denmark, larger numbers of patients have been reported. In these populations, odds ratios or hazard ratios can be calculated but they lack important detailed information about the dose, indication and co-medication.

Findings

Sexual function, reproductive hormones and fertility.

The effects of many immunosuppressive drugs on sexual function, reproductive hormones and fertility have not been properly evaluated. Many factors can contribute to this situation, for example, sperm samples are needed to evaluate sperm quality and this may lead to many logistic problems. In addition, there is a general misconception that male contributions to pregnancy are not important, which can contribute to a lack of interest by researchers and clinicians.

Furthermore, the effect of immunosuppressive drugs on sexual function, reproductive hormones and fertility cannot be studied separately. Multiple factors are interconnected in this process and should be considered in clinical practice and in future research.

Pregnancy and child outcomes.

The possible influence of paternal exposure before conception on pregnancy and child outcomes is also a neglected topic. In the last years, the number of publications has been increasing. In most cases, these studies include maternal and paternal exposures with little attention to the outcomes secondary to paternal exposure. Most of the time, no in-depth details of the paternal cases were available.

Strengths and limitations

The strengths of this study are based on the design and conduction of the systematic review. It followed strict pre-specified and reproducible methods. A comprehensive search strategy was developed to summarise the available information on many aspects of sexual health and reproduction. We did not restrict the search to a specific disease or drug (group) but tried to compile information about all important drugs (groups) used for several IMDs. Systematic reviews can also demonstrate where knowledge is lacking, and we consider that this is another major strength of this review. Major areas of opportunities for future research regarding this topic were identified.

Unfortunately, several limitations should be addressed. Most of the studies included small numbers of patients and controls. In addition, studies about sexual function, reproductive hormones and fertility in men with IMDs suffer from an inconsistent methodological quality; disease activity was not evaluated as a potential confounder in many studies; relevant comorbidities that also have a direct effect on these outcomes were not reported in all studies. Results might only apply to the specific populations studied.

Importantly, our findings should be interpreted with caution since a significant proportion of our included studies are case reports and small case series that tend to overestimate the outcomes of interest.

Regarding the pregnancy and child outcomes, the level of detail and specific information that is available in the publications needs to improve.

In this review, no animal studies were included. Animal studies show effects on reproductive outcomes for drugs such as methotrexate and thiopurines (Grosen *et al.*, 2017; Simsek *et al.*, 2018). Outcomes of animal studies are not always predictive for humans. Based on these outcomes and in addition to the lack of well-documented human paternal exposures in large studies, a restrictive wording is placed in the summary of product characteristics by the regulatory agencies.

Research recommendations

For many immunosuppressive drugs that are prescribed to millions of men with IMD, such as methotrexate or hydroxychloroquine, the possibility of re-evaluating their reproductive toxicity is of major importance and should be discussed. Semen analysis is still considered to be the most valid method to evaluate testicular toxicity in humans.

Ideally, RCTs and case–control well-designed prospective cohort studies should be designed to reach conclusive evidence.

While experimental studies are not ethical for assessing reproductive toxicity, observational studies such as those utilising case–control or cohort designs may be and should be considered. As a rule of thumb, if no increased incidence of malformations is observed within at least 1000 prospectively collected pregnancies, a conclusion might be reached that the drug of interest is not responsible for a 2-fold or more increase of the overall incidence of malformations (EMA, 2008).

Several factors such as the number of exposed patients, the incidence of the outcome in the unexposed control group, the minimum relative risk to be detected and the ratio of unexposed control to exposed study subjects can affect the power of a cohort study and should be considered during the early stages of a study design (Strom, 2020).

Focusing only on the prevalence of exposure and in order to put this into perspective, for frequently used drugs (>10% of the population), such as paracetamol, smaller sample sizes are needed to detect an increased risk of congenital malformations. For such drugs, the required sample size ranges from ∼8140 participants in a population cohort study to 614 participants in a case–control study. This range increases drastically for less frequently used drugs such as rituximab (<1% of the population), where ∼814 000 participants are needed in population cohort studies to 51 116 participants in case–control studies.

Based on these recommendations and following the example of the large Scandinavian cohorts here presented, collecting prospective data on current paternal exposures should be strongly recommended and considered for future research on this topic. In the meantime, health care professionals should think about these potential adverse events and intervene appropriately (see Table IV for research recommendations for standardisation).

Recently, it has been shown that disease activity can also impair fertility in men with rheumatic diseases (Villiger *et al.*, 2010; Ganatra *et al.*, 2018; Kaya Aksoy *et al.*, 2019; Perez-Garcia *et al.*, 2020). In consequence, it is very important to start focusing on developing well-designed epidemiological studies where study design and data analysis consider how diseases and drugs together can affect sexual health and reproduction.

To improve the overall quality of research on this topic, a call to action initiative that gets scientists from many different fields involved in the topic is needed. This could result in an organised plan to study and report future research.

Furthermore, access to information is more important than ever since effective communication has become an essential part of the treatment shared decision process between health care professionals and patients. Therefore, discussing the possible effect(s) of immunosuppressive drugs on male sexual health and reproduction should be considered for every man, irrespective of whether they have a wish to become a father or not.

Conclusion

There is little scientific evidence regarding the potential adverse events on male sexual function, reproductive hormones and fertility of many of the commonly used immunosuppressive drugs. Most of the included studies are heterogeneous and cannot be generalised to a wider population. With a lack of conclusive evidence, it is expected that clinicians and patients are confronted with difficult treatment decisions.

The results of this systematic review did not reveal major safety issues concerning paternal exposure to immunosuppressive drugs. However, we have to keep in mind that the numbers are low and an increased risk cannot be excluded. Well-designed and fully powered observational cohort studies with longitudinal data should be conducted to properly label these drugs. In cases where the number of patients included in a study is considered to be too low to reach

Table IV Research recommendations to conduct future research on these topics.

Sexual function	Use standardised screening questionnaires (IIEF). Case–control studies and well-designed prospective cohort studies are encouraged over cross-sectional studies. Consider relevant comorbidities and potential confounders e.g. depression, anxiety and disease activity.
Sperm quality	Use standardised methods to report sperm quality (WHO) (primary endpoint). DNA fragmentation index could provide more information regarding male fertility potential and should be considered as a secondary endpoint. Ideally, technicians should be blinded regarding the drug exposure. RCTs are ideal but case–control and well-designed prospective cohort studies are also encouraged over cross-sectional studies. Consider disease activity, relevant co-medication, comorbidities and potential confounders e.g. age, smoking and varicocele.
Reproductive hormones	Use standardised methods to measure hormones. RCTs are ideal but case–control and well-designed prospective cohort studies are also encouraged over cross-sectional studies. Consider disease activity, relevant comorbidities and potential confounders (age and co-medication)
Pregnancy and offspring outcomes	Collect data prospectively or report cases with all the relevant information, e.g. source of the information, indication, disease activity, clear description of medication use and timing (including co-medication) and paternal age. Regarding pregnancy/child outcomes, pregnancy outcome, gestational age, birth weight, infant health, genetic testing and follow-up period should be reported. The partner's relevant medical history should be considered.

adequate power, researchers should use standardised methods to measure outcomes of interest, ensure the quality of the collected variables and report their findings according to the STROBE statement (Vandenbroucke et al., 2007; von Elm et al., 2008). This will provide the scientific community with valuable information and allow it to perform meta-analyses in the future.

In cases of men with a wish to become a father, the sometimes very restrictive wording in the summary of product characteristics might not be necessary. In the meantime, in case the patient wishes to become a father, clinicians must discuss the pros and cons of stopping or changing drug treatment. The potential negative effects of the disease on reproductive outcomes and potential flares need to be weight against theoretical concerns of the drug effects.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Authors' roles

L.F.P-G., B.t.W., R.J.E.M.D. and W.B. contributed to the conception and study design. L.F.P-G. and B.t.W. analysed the data and contributed to the interpretation of the data. L.F.P-G. and B.t.W. wrote the first version of the manuscript and R.J.E.M.D., J.M.W.H., S.V., E.v.P. and W.B. revised it critically. All the authors read and approved the final manuscript.

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Conflict of interest

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