

Methotrexate

Selected References:

- American College of Obstetricians and Gynecologists. 2018. Tubal ectopic pregnancy. ACOG Practice Bulletin No. 193. *Obstet Gynecol* 131:e9—e103.
- Del Campo M, et al. 1999. Developmental delay in fetal aminopterin/methotrexate syndrome. *Teratology* 60:10-12.
- Donnenfield AE, et al. 1994. Methotrexate exposure prior to and during pregnancy. *Teratology* 49:79-81.
- Eck, LK, et al. 2017. Risk of adverse pregnancy outcome after paternal exposure to methotrexate within 90 days before pregnancy. *Obstet Gynecol* 129(4):707-714.
- Ersoy GS, et al. 2016. Comparison of the long-term effects of single-dose methotrexate and salpingectomy on ovarian reserve in terms of anti-müllerian hormone levels. *Human Fertility* 19(4):262-267.
- Feldkamp M, Carey JC. 1993. Clinical teratology counseling and consultation case report: low dose methotrexate exposure in the early weeks of pregnancy. *Teratology*; 47:533-439.
- French AE, et al. 2003. Effect of methotrexate on male fertility. *Can Fam Physician* 49:577-578.
- Friedman S, et al. 2017. Paternal use of azathioprine/6-mercaptopurine or methotrexate within 3 months before conception and long-term health outcomes in the offspring-A nationwide cohort study. *Reprod Toxicol* 73:196-200.
- Gubatan J, et al. 2023. Paternal medications in inflammatory bowel disease and male fertility and reproductive outcomes: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 21(9):2222-2238.
- Hoeltzenbein M, et al. 2008. Paternal exposure to drugs—is there an increased risk for congenital abnormalities? Experience of the Berlin Institute for Clinical Teratology and Drug Risk Assessment during Pregnancy. *Reprod Toxicol* 26: 64 [abstract].
- Hyoun SC, et al. 2012. Teratogen update: methotrexate. *Birth Defects Res A Clin Mol Teratol*, 94(4):187-207.
- Jordan RL, et al. 1976. Embryotoxicity of the folate antagonist methotrexate in rats and rabbits. *Teratology* 15:73-80.
- Kozlowski RD, et al. 1990. Outcome of first-trimester to low-dose methotrexate in eight patients with rheumatic disease. *Am J Med* 88(6):589-592.
- Lee CY, et al. 2010. A pilot study of paternal drug exposure: the Motherisk experience. *Reprod Toxicol*. 29(3):353-60.
- Lloyd ME, et al. 1999. The effects of methotrexate on pregnancy, fertility and lactation. *Q J Med* 92:551-563
- Martin M.C., et al. 2014. Methotrexate embryopathy after exposure to low weekly doses in early pregnancy. *Reprod Toxicol*, 43: 26-29.
- Martínez Lopez JA, et al. 2009. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy and breastfeeding). *Clin Exp Rheumatol* 27:678-684.
- McLaren JF, et al. 2009. Effect of methotrexate exposure on subsequent fertility in women undergoing controlled ovarian stimulation. *Fertil Steril* 92(2):515-519.
- Methotrexate Drug Label, 2020:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/040054s015,s016,s017.pdf.
- Nagafuchi H, et al. 2022. Pregnancy outcomes in patients with rheumatoid arthritis who discontinue methotrexate treatment to conceive. *Clin Rheumatol*; 41(3):669-675.
- Ostensen M, et al. 2009. Management of RA medications in pregnant patients. *Nat Rev Rheumatol* 5(7):382-390.
- Wentzell N, et al. 2023. Use of methotrexate in girls and women of childbearing age, occurrence of methotrexate-exposed pregnancies and their outcomes in Germany: A Claims Data Analysis. *Clin Drug Investig*. 43(2):109-117.

- Zanetti A, et al. 2022. Impact of rheumatoid arthritis and methotrexate on pregnancy outcomes: retrospective cohort study of the Italian Society for Rheumatology. *RMD Open*; 8(2):e002412.
- Zarén P, et al. 2023. Methotrexate use among men-association with fertility and the perinatal health of their children: a Swedish nationwide register study. *Fertil Steril*. 120(3 Pt 2):661-669.

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Selected References

- Andersen AN, et al. 2002. Fever in pregnancy and risk of fetal death: a cohort study. *The Lancet* 360: 1552-1556.
- Antoun S, et al. 2021. Fever during pregnancy as a risk factor for neurodevelopmental disorders: results from a systematic review and meta-analysis. *Molecular Autism*. 12: 1-13.
- Auger N, et al. 2017. Risk of congenital heart defects after ambient heat exposure early in pregnancy. *Environ Health Perspect*; 125(1):8-14.
- Basagaña X, et al. 2021. Low and high ambient temperatures during pregnancy and birth weight among 624,940 singleton term births in Israel (2010-2014): an investigation of potential windows of susceptibility. *Environmental Health Perspectives* 129.10: 107001.
- Botto LD, et al. 2013. National Birth Defects Prevention Study. Congenital heart defects after maternal fever. *Am J Obstet Gynecol*. 210(4):359. e1-359.e11.
- Chambers CD, et al. 1998. Maternal fever and birth outcome: a prospective study. *Teratology*. 58:251-257.
- Chambers CD 2006. Risks of hyperthermia associated with hot tub or spa use by pregnant women. *Birth Defects Reseach (part A)* 76:569-573.

- Dreier JW, et al. 2014. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. *Pediatrics*.133(3):e674-688.
- Duong, et al. National Birth Defects Prevention Study. 2011. Maternal use of hot tub and major structural birth defects. *Birth Defects Res A Clin Mol Teratol*. 91(9):836-841.
- Edwards MJ, et al. 1995. Hyperthermia and birth defects. *Reprod Toxicol* 9(5):411.
- Evenson DP, et al. 2000. Characteristics of human sperm chromatin structure following an episode of influenza and high fever: a case study. *J Androl*. 21:739-46.
- Graham JM Jr, et al. 1998. Teratogen update: gestational effects of maternal hyperthermia due to febrile illnesses and resultant patterns of defects in humans. *Teratology*; 58:209-21.
- Graham JM Jr 2020. Update on the gestational effects of maternal hyperthermia. *Birth Defects Research* 112.12:943-952.
- Harvey MAS, et al. 1981. Suggested limits to the use of hot tub and sauna by pregnant women. *CMAJ* 125:50.
- Hashmi, SS et al 2009. Maternal fever during early pregnancy and the risk of oral clefts. *Birth Defects Research (part A)* 88:186-194.
- Hornig M, et al. 2018. Prenatal fever and autism risk. *Molecular Psychiatry*. 23.3: 759-766.
- Keister, et al. 2008. Strategies for breastfeeding success. *Am Fam Physician* 78(2): 225-232.
- Kerr S, Parker SE, et al. 2017. Preconceptional maternal fever, folic acid intake and the risk for neural tube defects. *Annals of Epidemiology* 27:777.
- Layde PM, et al. 1980. Maternal fever and neural tube defects. *Teratology* 21:105.
- Lawrence RM and Lawrence RA (2001). Given the benefits of breastfeeding, what contraindications exist? *Pediatric Clinics of North America* 48(1):235-251.
- Leshtinski I, et al. 2022. Risk of Autism Spectrum Disorder in Offspring Following Exposure to Maternal Fever during Pregnancy: A Systematic Review and Meta-Analysis. *Progress in Medical Sciences*. 6(2):1-8.
- Lipson A, et al. 1985. Saunas and birth defects. *Teratology* 32:147.
- Lyndberg MC, et al. 1994. Maternal flu, fever, and the risk of neural tube defects: A population based case-control study. *Am J Epidemiol* 140(3):244.
- Milunsky A, et al. 1992. Maternal heat exposure and neural tube defects. *JAMA* 268(7):882.
- Moretti ME, et al. 2005. Maternal hyperthermia and the risk for neural tube defects in offspring: Systematic review and meta-analysis. *Epidemiol*.16:216-219. NCRP. 1983. National Council on Radiation Protection and Measurements Report No 74, Bethesda, MD, 72.
- Nybo Anderson, AM 2002. Fever in pregnancy and risk of fetal death: a cohort study. *Lancet* 360:1152-1556.
- Ridge BR and Budd GM. 1990. How long is too long in a spa pool? *NEJM* 323(12):835.
- Ravanelli N, et al. 2019. Heat stress and fetal risk. Environmental limits for exercise and passive heat stress during pregnancy: a systematic review with best evidence synthesis. *British journal of sports medicine* 53(13): 799-805.
- Sass L, et al. 2017. Fever in Pregnancy and the Risk of Congenital Malformations: a Cohort Study. *BMC Pregnancy and Childbirth* 17:413
- Sanford MK, et al. 1992. Neural tube defect etiology: Evidence concerning maternal hyperthermia, health and diet. *Dev Med Child Neurol* 34:661.
- Sun S, et al. 2019. Ambient temperature and markers of fetal growth: a retrospective observational study of 29 million US singleton births. *Environmental Health Perspectives* 127.6: 067005.
- Thonneau P, et al. 1998. Occupational heat exposure and male fertility: a review. *Human reproduction* 13(8):2122-2125.
- Vahedian-Azimi A, et al. Does SARS-CoV-2 Threaten Male Fertility? *Clinical, Biological and Molecular Aspects of COVID-19*. 139-146.
- Warkany J. 1986. Teratogen Update. Hyperthermia. *Teratology* 33:365.
- Werenberg Drier J, Nybo Andersen AM, et al. 2014. Systematic Review and Meta-analyses: Fever in Pregnancy and Health Impacts in the Offspring. *Pediatrics* 133(8):e675

- Wertheimer N and Leeper E. 1986. Possible effects of electric blankets and heated waterbeds on fetal development. *Bioelectromagnetics* 7:13.
- Zhang MH et al, 2018. Impact of a mild scrotal heating on sperm chromosomal abnormality, acrosin activity and seminal alpha-glucosidase in human fertile males. *Andrologia*. 50:1–12.

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Methotrexate

Selected References:

- Absalan, F., Ghannadi, A., & Zabihi, A. (2014). The effects of different doses of ketamine on quality of normal ejaculated sperm. *International journal of fertility & sterility*, 8(2), 207–214.
- American College of Obstetricians and Gynecologists (ACOG). 2018. Committee Opinion No. 753: Assessment and Treatment of Pregnant Women with Suspected or Confirmed Influenza. *Obstet Gyn.* 132(4):e169-e173.
- Andrade C. 2017. Ketamine for Depression, 2: Diagnostic and Contextual Indications. *J Clin Psychiatry*. 78(5):e555-e558.
- Bai X, et al. 2013. Ketamine enhances human neural stem cell proliferation and induces neuronal apoptosis via reactive oxygen species-mediated mitochondrial pathway. *Anesth Analg.* 116(4):869-80.
- Baraka A, et al. 1990. Maternal awareness and neonatal outcome after ketamine induction of anaesthesia for caesarean section. *Can J Anaesth* 37:641-4.
- Brambrink AM, et al. 2012. Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. *Anesthesiology*. 116(2):372-84.
- Capitanio JP, et al. 2012. Behavioral effects of prenatal ketamine exposure in rhesus macaques are dependent on MAOA genotype. *Exp Clin Psychopharmacol.* 20(3):173-80.
- Cheung HM, et al. 2017. How Ketamine Affects Livers of Pregnant Mice and Developing Mice? *Int J Mol Sci.* 18(5). pii: E1098.
- Cheung, HM, & Yew, D. T. W, et al 2019. Effects of Perinatal Exposure to Ketamine on the Developing

Brain. *Frontiers in neuroscience*, 13, 138.

- Chomchai S, et al. 2019. Effects of unconventional recreational drug use in pregnancy. *Semin Fetal Neonatal Med.* pii: S1744-165X (19)30019-8.
- Corssen G. 1974. Ketamine in obstetric anesthesia. *Clin Obstet Gynecol* 17:249-58.
- Dong C, et al. 2016. Ketamine exposure during embryogenesis inhibit cellular proliferation in rat fetal cortical neurogenic regions. *Acta Anaesthesiol Scand.* 60(5): 579-587.
- Galbert MW, Gardner AE. 1973. Ketamine for obstetrical anesthesia. *Anesth Analg.* 52:926-30.
- Galloon S. 1976. Ketamine for obstetric delivery. *Anesthesiology* 44:522-4.
- Gilder, M. E., Tun, N. W., Carter, A., Tan, F. F. S. L., Min, A. M., Eh, H., Aye, P., Carrara, V. I., Angkurawaranon, C., & McGready, R. (2021). Outcomes for 298 breastfed neonates whose mothers received ketamine and diazepam for postpartum tubal ligation in a resource-limited setting. *BMC pregnancy and childbirth*, 21(1), 1
- Janeczko GF, et al. 1974. Low-dose ketamine anesthesia for obstetrical delivery. *Anesth Analg.* 53:828-31.
- Ketalar. Product labeling. 2020.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/016812s046lbl.pdf
- Kocum A, et al. 2012. Spinal anesthesia under sedation using propofol and ketamine for laparoscopic cholecystectomy in a patient during 13th week of gestation. *J Anesth.* 26(4):634-635.
- Krissel J, et al. 1994. Thiopentone, thiopentone/ketamine, and ketamine for induction of anaesthesia in caesarean section. *Eur J Anaesthesiol* 11:115-22.
- Little B, et al. 1972. A study of ketamine as an obstetric anesthetic agent. *Am J Obstet Gynecol.* 113:247.
- Majdinasab, E., Datta, P., Krutsch, K., Baker, T., & Hale, T. W et. 2023. Pharmacokinetics of Ketamine Transfer Into Human Milk. *Journal of clinical psychopharmacology*, 43(5), 407-410.
- Meer FM, et al. 1973. An intravenous method of anaesthesia for caesarean section. Part II: ketamine. *Br J Anaesth.* 45:191-6.
- Moore J, et al. 1971. Preliminary report on ketamine in obstetrics. *Br J Anaesth* 43:779-82, 1971.
- Ortega D, et al. 1999. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. *Acta Anaesthesiol Scand.* 43:394-7.
- Oats JN et al. 1979. Effects of ketamine on the pregnant uterus. *Br J Anaesth* 51:1163-6.
- Potter J, et al. 2019. A combination of inhaled nitrous oxide and low-dose ketamine infusion for labor analgesia. *J Clin Anesth.* 12;57:64-65.
- Sassano-Higgins S, et al. 2016. A Review of Ketamine Abuse and Diversion. *Depress Anxiety.* 33(8):718-27.
- Slikker W Jr, et al. 2007. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. *Toxicol Sci.* 98(1):145-158.
- Su PH, et al. 2010. Infant with in utero ketamine exposure: quantitative measurement of residual dosage in hair. *Pediatr Neonatol.* 2010. 51(5):279-84.
- Talahma M, et al. 2018. Ketamine infusion used to successfully control refractory status epilepticus in a pregnant patient. *Case Rep Neurol Med.* 3041279.
- Wolfson P, et al. 2022. The pharmacokinetics of ketamine in the breast milk of lactating women: Quantification of ketamine and metabolites. *J Psychoactive Drugs.* 2022:1-5.

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Methotrexate

Selected References:

- Alwan NA, et al. 2015. Maternal iron status in early pregnancy and birth outcomes: insights from the Baby's Vascular health and Iron in Pregnancy study. *Br J Nutr* 113(12):1985-1992.
- Baker et al, 2010. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics* 126(5):1040-1050.
- Blot I, et al. 1999. Iron deficiency in pregnancy: effects on the newborn. *Curr Opin Hematol* 6:65-70.
- Chavarro JE, et al. 2006. Iron intake and risk of ovulatory infertility. *Obstet Gynecol* 108:1145-1152.
- Georgieff MK, et al. 1994. Reduced neonatal liver iron stores following prenatal uteroplacental insufficiency (UPI). *Pediatr Res* 35:312A.
- Haider BA, et al. 2013. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 346:f3443.
- Heinonen OP, et al. 1977. *Birth Defects and Drugs in Pregnancy*, Littleton, Publishing Sciences Group.
- Kasperczyk A, et al. 2016. Influence of iron on sperm motility and selected oxidative stress parameters in fertile males – a pilot study. *Ann Agric Environ Med* 23(2):292-296.
- Kullander S, Kallen B. 1976. A prospective study of drugs and pregnancy. 4. Miscellaneous drugs. *Acta Obstet Gynecol Scand* 55:287-295.
- Kundak AA, et al. 2017. Do toxic metals and trace elements have a role in the pathogenesis of conotruncal heart malformations? *Cardiol Young* 27(2): 312-317.
- Martinex-Galiano JM, et al. 2019. Maternal iron intake during pregnancy and the risk of small for gestational age. *Matern Child Nutr* 15(3): e12814.
- McElhatton PR, et al. 1991. The consequences of iron overdose and its treatment with desferrioxamine in pregnancy. *Hum Exp Toxicol* 10:251-259.
- National Institutes of Health Office of Dietary Supplements. 2023. Iron: Fact Sheet for Health Professionals. Available at: <https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/>. Accessed 22 July 2024.
- Nelson MM, Forfar Jo. 1971. Associations between drugs administered during pregnancy and congenital anomalies of the fetus. *Br Med J* 1:523-527.
- Olenmark M, et al. 1987. Fatal iron intoxication in late pregnancy. *J Toxicol Clin Toxicol* 25:347-360.
- Singla PN, et al. 1996. Fetal iron status in maternal anemia. *Acta Paediatr* 85: 1327-1330.
- Tran T, et al. 2000. Intentional iron overdose in pregnancy-management and outcome. *J Emerg Med* 18:225-228.
- United States Department of Agriculture. USDA National Nutrient Database for Standard Reference Legacy for Iron. Available at: <https://www.nal.usda.gov/sites/default/files/page-files/iron.pdf>. Accessed 22 July 2024.
- World Health Organization. Guideline: Daily Iron Supplementation in adult women and adolescent girls. Available at: https://iris.who.int/bitstream/handle/10665/204761/9789241510196_eng.pdf. Accessed 22 July

2024.

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Selected References:

- Ban L, et al. 2014. First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. PLoS One; 9(6):e100996.
- Dusci LJ, et al. 1990. Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam. Br J Clin Pharmacol; 29:123-6.
- Kanto JH. 1982. Use of benzodiazepines during pregnancy, labour and lactation, with particular reference to pharmacokinetic considerations. Drugs 23:354-80.
- Kargas GA, et al. 1985. Perinatal mortality due to interaction of diphenhydramine and temazepam. N Eng J Med 313:1417-8.
- Kelly LE, et al. Neonatal benzodiazepines exposure during breastfeeding. J Pediatr. 161:448-51.
- Lebedevs TH, et al. 1992. Excretion of temazepam in breast milk. Br J Clin Pharmacol; 33:204-6.
- Restoril Prescribing Information. Available online at www.accessdata.fda.gov/drugsatfda_docs/label/2016/018163s064lbl.pdf. [Accessed May 2025].
- Sheehy O, et al. 2019. Association between incident exposure to benzodiazepines in early pregnancy and risk of spontaneous abortion. JAMA psychiatry, 76(9): 948-57.
- Szpunar MJ, et al. 2022. Risk of major malformations in infants after first-trimester exposure to benzodiazepines: Results from the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications. Depression and Anxiety 39.12: 751-9.

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