

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.
- Zarán 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
- Sandford 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.
- Martinez-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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