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Carbon Disulfide (CS_2) Exposure and Human Reproductive Health- A Narrative Overview

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Abstract

Carbon disulfide is one of the important solvents and is utilized in the manufacture of carbon tetrachloride, cellophane, rayon, rubber and is used extensively as a solvent in various processes etc. The long-term exposure to CS_2 might be related to certain adverse health outcomes. The data were gathered with respect to CS_2 exposure and human reproductive health and outcome through the internet by searching various websites. The data available pointed out that women workers who were exposed to CS_2 in the workplace for a longer duration of time may experience adverse effects on menstruation patterns and might affect the reproductive health of the exposed workers. While its exposure may deteriorate the semen quality based upon the studies available mainly on viscose rayon factory workers exposed to CS_2 occupationally. Some inadequate data are also available on alterations in reproductive hormonal levels in CS_2 exposed workers. However, more data are necessary on the impact of CS_2 exposure on human reproduction and pregnancy outcomes as additional precise data are needed with regards to exposure and affect parameters with reverence to CS_2 exposure. However, positive hostile impact data on CS_2 exposure on certain reproductive endpoints indicate reducing/checking/preventing workers from exposure to CS_2 in the workplace to protect the worker's reproductive health or pregnancy outcome.

Keywords: Carbon disulfide; Reproductive health; Semen analysis; Sperm motility; Hormones

Introduction

Carbon disulfide (CS_2) looks as a clear colorless to light yellow volatile liquid, industrial and reagent grades are having unpleasant odor. It is insoluble in water, and it is denser than water. Furthermore, vapors are heavier compared to air. It is utilized in the production of rayon and cellophane, flotation agents and used as a solvent extensively (1). Human are exposed to CS_2 mainly in rayon fiber, cellophane manufacture, and it is utilizing as solvent in various process etc. Earlier, Sakurai conducted a morbidity study among viscose rayon factory workers those were exposed to CS_2 occupationally and stated that renal and hypertensive diseases were considerably more frequent among the rayon' spinners and cutters with 10 years or more exposure, in the highly exposed group, compared to the non-exposed or control workers. When the non-exposed and the negligible CS_2 exposed workers are taken together as a reference group, the ischemic heart illness was substantially higher in the most highly CS_2 exposed group than this complication in the reference group (2). Later, Schramm *et al*. evaluated Intima-media thickness of the carotid arteries (IMT) which is an recognized indicator of atherosclerosis and a reasonable indicator for cardiovascular hazard in a cohort of CS_2 exposed employees and concluded that long-duration CS_2 exposure is a risk factor for IMT changes, and workers exposed to >10 ppm of CS_2 at least 3 years showed a substantial elevation in IMT indicating CVD risk in CS_2 exposed workers (3).Furthermore, Domergue *et al.* stated no proof of cardiovascular toxicity among CS_2 exposed workers below 5 ppm of CS_2 concentration at workplace environment (4).

Earlier, USEPA summarized that exposure to CS_2 generally occurs mostly through occupationally. Acute exposure to CS_2 through inhalation may cause alterations in breathing and causes chest pains. Nausea, dizziness, fatigue, vomiting, headache, lethargy, blurred vision, mood changes, delirium, and convulsions have been described in humans exposed to CS_2 by inhalation. Furthermore, neurologic effects, involving behavioral and neurophysiological variations, have been documented in chronic (long-duration) exposure to CS_2 in both from human and animal studies. Moreover, reproductive hostile effects, such as diminished sperm count and menstrual disturbances, also reported in humans due to CS_2 exposure**.** Earlier, Takebayashi *et al.* studied to understand the present level of CS_2 exposure is adequate to stop occurrence of subclinical health impairments or to amend health impacts owing to earlier higher exposure. They reported that out of a total of 54 subjective symptoms studied many of them were increased like, heavy sensation in the head, fainting after sudden standing, light headedness, tremor, dullness, and sensitivity elevation of skin in the extremities, lower grasping power, lower sexual desire, and augmented rough skin. They further mentioned that subclinical impacts on the nervous system and glucose metabolism were noticed in the CS_2 exposed workers. One of the explanations was that considerable higher CS_2 exposure in the past may cause these changes, but these consequences were still not amended under the current CS_2 exposure. Another probability was suggested that the current CS_2 exposure may produce these changes (6). In addition, Stetkiewicz and Wrońska-Nofer asserted that clinical studies published in 1995-1997 did not provide evidence of hostile effects on the cardiovascular and neurological systems in CS_2 exposed workers at a concentration lower to 48 mg/m^3.The harmful impacts of low level of CS_2 exposure on the reproduction have not confirmed that CS_2 adversely distresses the embryo and the fetus (7). However, industrial exposure to CS_2 may be linked with reproductive health deterioration in

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human beings exposed to CS_2 chronically. Hence the present overview is prepared with the view to present the current information on impact of CS_2 exposure on human reproductive health and on pregnancy outcome as no comprehensive overview is accessible on this point of human reproduction.

Material and Methods

The literature was collected through using internet by searching various websites such as Google, Google Scholar, PubMed, PubChem, etc. using various key words related to the theme of this MS like carbon disulfide and male reproduction, libido, semen quality, sperm motility, count, sperm DNA damage etc. and carbon disulfide and female reproduction, hormonal changes, menarche, puberty, menstruation, and menopausal age, etc. Some of the general information on carbon disulfide and toxicity was also collected and relevant information were included in this overview. The papers were not included in this communication whose even abstracts were not available in English language or with incomplete bibliography. The old papers those published prior to 1980 were also not included in this communication to provide recent view on this subject of human reproduction. The overview is separated into two broad sections 1) Carbon disulfide and male reproduction, semen quality etc. and 2) Carbon disulfide and female reproduction, pregnancy, or its outcome. The data were also compiled in table 1 and 2 for better and quick understanding of the relevant available information on this subject.

Results and Discussion

Several reports are available on long-duration carbon disulfide exposure at workplace and deterioration of health of the CS_2 exposed workers. Gelbke *et al.* stated that the most imperative health impacts of carbon disulfide are coronary heart ailment, coronary risk factors, color discrimination, retinal angiopathy, psychophysiological effects, impacts on peripheral nerves, morphological and other central nervous system impacts, fertility, and hormonal impacts in CS_2 exposed workers (8). Furthermore, WHO reviewed that there are numerous reports of diminished libido and/or impotence in male workers exposed to high concentrations of CS_2 at work environment but there is no consistent evidence for other adverse reproductive effects in human because limited study carried out on other reproductive endpoints. In experimental animals, CS_2 is reported to have embryo and fetotoxic potential at high concentrations [9]. Later, Silva stated that Sodium tetrathio-carbonate (STTC) is a pesticide when it is prepared for usage in aqueous solution, it produces two toxic products i.e., CS_2 and hydrogen sulfide resulting for potential exposure of workers from these chemicals. They asserted that STTC did not cause developmental or reproductive hostile impacts in animal studies. While CS_2 was found to be a developmental and neurobehavioral toxin to rat pups and reproductive adverse effects happened in workers of both sexes with CS_2 exposure (10). Some data are available on exposure to CS_2 with respect to male and female human reproductive health with inconsistence findings. Reasonable data are available on semen quality and menstrual disorders among female workers with respect to CS_2 exposure in occupational situations. However, data on other reproductive endpoints with respect to CS_2 exposure are very scanty or not available.

Carbon disulfide and Male reproduction, Semen quality

Several experimental controlled animal studies are available on CS_2 exposure and its hostile impact upon testicular tissues and sperm quality of experimental animals (Tepe and Zenick 1984, Zenick *et al.* 1984, Kumar *et al.*1999, Tang and Xuan 2003, Chen *et al.*2005, Guo *et al.* 2014) (11-16). A few published clinical reports are also available on CS_2 exposure in workplace and alteration in male reproductive health especially semen quality. Earlier, Vanhoorne *et al.* enrolled male viscose rayon factory workers exposed to CS_2 and other workers, those were not subjected to any toxic compound in the working environment. They were interviewed for their sexual conduct and reproductive history. The results indicated a significant influence of CS_2 exposure on libido and potency, while no significant effects were noted on fertility or semen quality (17). Later, Ma *et al*. described the effects of work-related CS_2exposure on sexual task and semen quality. The level of sexual impairment was greater, number of sexual encounters was fewer, and duration of sexual encounters was briefer in CS_2 exposed workers compared to the control. The difference in these parameters was statistically significant. Furthermore, exposed workers had lower semen quality, lower acrosomal membrane integrity rate, lengthier liquefaction time, low sperm density, vitality, and significantly more abnormality of semen in exposed workers than control (18). Earlier, Batora *et al.* stated that manifestation of erectile dysfunction (ED) among workers of viscose rayon who were exposed chronically to CS_2 was established as an occupational illness and evaluated the effectiveness of sildenafil treatment in subjects with ED associated with chronic CS_2 intoxication. The treatment with sildenafil substantially enhanced the ability to accomplish and maintain an erection in all subgroups of men with ED (age, duration of ED, duration of CS_2 exposure and antidepressant medication) (19). Earlier, Takebayashi *et al.* stated reduced sexual desire and symptoms linking to disturbance of sexual behavior in the CS_2 exposed workers (6).

Later, Guo *et al*. analyzed the association amid work-related exposure to CS_2 and male reproductive impairments and stated that CS_2-exposed laborers had considerably higher serum concentrations of luteinizing hormone, follicle-stimulating hormone levels, and lower concentrations of testosterone compared to control workers. A significant decline was also noted in sperm motility, viability, mitochondrial membrane potential, chromatin antioxidant capacity, in CS_2 exposed workers (20). Earlier, Jensen *et al*. reviewed that the evidence of hostile consequence of various occupational, environmental exposures, toxicants, like excessive heat, inorganic lead, di-bromochloropropane, ethylene glycol ethers, ethylene dibromide, CS_2, ionizing radiation, and welding operations on male reproduction, is supported by several epidemiological studies. For other agents, the association is only suspected and needs further study (21). Furthermore, Schrag and Dixon also stated that agents with confirmed hostile effects on male reproduction include di-bromochloropropane, lead, carbon disulfide, and oral contraceptives (22).

Earlier, Wagar *et al.* stated that FSH levels were considerably greater among the CS_2 exposed men compared to control (13.6 vs 10.0 IU/l). While the level of sex hormone binding globulin was substantially lesser among the CS_2 exposed men than control. Men age with 40 year or more, with a minimum of 10 yrs. of CS_2 exposure, only LH and FSH were considerably greater than in the controls. Although the observed alterations do not appear to have any obvious clinical implications among the study groups, they stated that levels of CS_2 were lower than the Finnish threshold level (30 mg/m^3) may affect the hormonal equilibrium in the pituitary-gonadal axis, supporting the opinion that there may be an elevated hazard of latent primary gonadal insufficiency (23). Earlier, they examined the effect of long-term occupational CS_2

exposure (10 and 36 yr.) on endocrinologic parameters of male workers. The CS_2 levels in the rayon factory was lower than the Finnish threshold i.e., 30 mg/m^3 (10 ppm) level for the last 10 yr. Prior to this the CS_2 exposure was considerably greater. They found serum FSH, and LH were substantially higher in the exposed group. No disturbance was seen in thyroid function as assessed by serum thyroxine (T_4), free thyroxine index (FTI), triiodothyronine (T_3), and the thyrotropin response to TRH level. Serum cortisol level was also not altered. These suggest that earlier higher CS_2 exposure rather than present exposure to low CS_2 concentrations might be related to these alterations **(Wägar *et al.*** (24)**.** Furthermore, Meyer studied the semen quality of CS_2 exposed workers and control subjects from the same industry and reported that there were no considerable changes in semen quality parameters between exposed and controls at current CS_2 exposure levels (25).

Owing to the toxic potential of CS_2 on male reproduction including sperm quality, it is rational to consider the occurrence of male mediated hostile reproductive outcome in female due to CS_2 exposure of their partner. However, data are scanty or inadequate on this aspect of human reproduction. Patel *et al*. examined male workers exposed to CS_2, those were employed ten years or more preceding to the study to assess the impacts of industrial exposure of CS_2 on the reproductive functions with emphasis on miscarriages in their wives. They reported that the incidences of number of miscarriages against number of living children correlated well with environmental concentration of CS_2 in the workplace. Furthermore, the occurrences of miscarriage rates were 5.7% while the mean levels of CS_2 were 1.69 ppm. When environmental concentrations of CS_2 were 12.28 ppm than the occurrences of miscarriages were18.9% (26). In addition, Chang *et al.* investigated impact of carbon disulfide exposure on couple fecundability by measuring time to pregnancy (TTP) and recruited a total of 56 male workers from the rayon industry. The data revealed that the CS_2 exposure had a considerably harmful impact on male fecundability, particularly with long duration and more CS_2 exposure (27). More in-depth studies are needed on CS_2 exposure to male and its impact upon pregnancy outcome. The data accessible on CS_2 exposure and human male reproduction particularly from workers of viscose rayon industry exposed to CS_2 suggested that long-term high doses of CS_2 exposure for a longer duration might be related with sexual dysfunction and deterioration of semen quality.

Carbon disulfide and female reproduction, pregnancy, or its outcome

Several experimental reports are available on exposure to CS_2 and female reproductive health and embryonic growth or, pregnancy outcome (Saillenfait *et al.*, ATSDR, Tsai *et al.*, Yang *et al.*) (28-31)**.**

Table 1: Carbon disulfide exposure and Male reproduction, Semen quality

Sl No	Exposure/Subjects	Effects	References
1	Male viscose rayon workers exposed to CS_2.	A significant impact of CS_2 on libido & potency, but no significant effects on fertility or semen quality.	Vanhoorne *et al.*
2	Work-related CS_2 exposure and sexual function & semen quality.	More sexual dysfunction, less sexual encounters & length was shorter in CS_2 exposed workers. Exposed workers showed with low semen quantity, lower acrosomal membrane integrity, density & vitality, more semen deformity & longer liquefaction time,	Ma *et al*.
3	Viscose rayon workers & chronic CS_2 exposure	Erectile dysfunction exposed to CS_2 in rayon workers acknowledged as an industrial illness.	Batora *et al.*
4	CS_2 exposed worker	Reduced sexual desire & disturbance of sexual behavior	Takebayas-hi *et al.*
5	Assessed association amid work-related CS_2 exposure & male reproductive damage	A considerably higher serum levels of FSH, LH, & lower testosterone levels in CS_2-exposed workers. A significant decline in sperm motility, viability, chromatin, antioxidant capacity, & mitochondrial membrane potential.	Guo *et al*.
6	CS_2 exposed men.	FSH levels was significantly higher while sex hormone binding globulin level was significantly lower in CS_2 exposed men.	Wagar *et al.*
7	Long-term CS_2 exposure (10 & 36 yrs) on endocrinologic parameters of male workers.	CS_2 levels in rayon plant was lower than Finnish threshold i.e., 30 mg/m^3 (10 ppm) for the past 10 yrs. Prior to this CS_2 level was greater. Serum FSH, & LH were significantly more while no disruption seen in thyroid function as assessed by serum thyroxine, free thyroxine index, triiodothyronine, & thyrotropin response to TRH level. Serum cortisol level was not altered.	Wägar *et al*.
8	Semen quality in CS_2 exposed workers.	No significant variations in semen quality amid exposed & control subjects.	Meyer
9	Male mediated hostile reproductive outcomes in CS_2exposed rayon workers	When mean CS_2levels were 1.69 ppm, the miscarriages rate was 5.71%.While when CS_2 concentrations were 12.28 ppm than miscarriage was 18.91%.	Patel *et al*.
10	CS_2 on couple fecundability by assessing time to pregnancy & recruited male workers from rayon industry.	CS_2 exposure had a considerably harmful impact on male fecundability, particularly with long duration and higher CS_2 exposure	Chang *et al.*

FSH-follicle-stimulating hormone; LH-luteinizing hormone

A few clinical reports are also available on the impact of CS_2 exposure on human female reproduction, menstrual disorder, pregnancy, and its outcome in occupational settings. Earlier, Zhou *et al*. conducted a study among female workers

exposed to CS_2 and non-exposed workers. The workers who were exposed to CS_2 with mean of 1.7-14.8 mg/m^3 of CS_2 for about 15 years. The data indicated that CS_2 exposed workers had a considerably greater manifestation of menstrual disorder than women of the non-exposed group (35.9% vs. 18.2%). No substantial variation was observed between exposed and non-exposed subjects with respect to occurrence of toxemia, emesis gravidarum, stillbirth, spontaneous abortion, overdue and premature delivery, or congenital malformation. These findings indicated that CS_2 exposure at about 10 mg/m^3 might impact the female reproductive function (32). Furthermore, Cai and Bao mentioned that CS_2 in air was found to be 37-56 mg/m^3 in the environment of rayon factories where, female spinners exposed to CS_2 revealed more incidence of menstrual cycle impairment and pregnancy toxemia compared to the non-exposed workers. The umbilical blood of spinner contained 5 µg/100 ml of CS_2. Milk from breast-feeding spinners during working hours was contained 2.8-18.6 µg/100 ml of CS_2. They suggested that the exposure to higher concentration of CS_2 may alter the maternal function of female workers, and CS_2 can reach into the fetuses via the placenta or babies through mother milk (33).

Pieleszek studied the impact of CS_2 exposure on menopause, level of monoamines, gonadotropins, estrogens, and androgens in women. The studies were conducted among 199 women comprising the control group I) 80 women from the industrial clothing factory without CS_2 exposure and exposed group II) 119 women workers from the synthetic fibers factory exposed to CS_2 with a concentration of ~9.36-23.4 mg/m^3. Menopause observed in 16.59% of CS_2 exposed women workers, compared to 8.05% of control women workers. In a retrospective analysis among menopausal women of exposed group showed a statistically considerable elevation in abortion and menstrual cycles disorders. The CS_2 exposed women also had significantly more weight gain, headaches, and libido loss. The serum estrone, progesterone, estradiol, 17-hydroxyprogesterone levels were lower considerably in women who were exposed to CS_2. While no significant variations in FSH or LH level was noted between exposed and controls (34). Health Council of the Netherlands evaluated studies available on CS_2 and human reproductive health and suggested that occupational exposure to CS_2 may cause menstrual disorders and affect pregnancy or its outcome. However, inconsistent results, poor reporting, and lack of valid information on control groups and lack of actual exposure levels data hamper a proper evaluation.

Table 2: Carbon disulfide and Female Reproduction, Pregnancy, or its outcome

Sl. No.	Exposure/Subjects	Effects	References
1	Female workers exposed to CS_2 (CS_2 level~ 1.7-14.8 mg/m^3)	A significantly more menstrual disorder in exposed workers. No significant variation amid exposed & non-exposed with regards to toxemia, emesis gravidarum, spontaneous abortion, stillbirth, overdue or premature delivery, congenital malformation. Exposure to CS_2 ~10 mg/m^3 might affect female reproductive function	Zhou *et al*. (1988)
2	Impact of CS_2 on menopause, level of monoamines, gonadotropins, estrogens, & androgens	Menopause noted in 16.59% CS_2 exposed women, compared to 8.05% in control. In a retrospective analysis among menopausal women of exposed group showed a statistically considerable elevation in abortion and menstrual cycles disorders. Exposed women had more headaches, weight gain & loss of libido. The serum estrone, estradiol, progesterone, 17-hydroxyprogesterone were lower in exposed women while no significant variations noted in FSH, LH level.	Pieleszek (1997)
3	Evaluated studies on CS_2 & human reproductive health	CS_2 exposure may cause menstrual disorders & affect pregnancy or outcome. Though, inconsistent results, poor reporting, lack of valid information on control & exposure data hamper proper evaluation.	Health Council of the Netherlands (2011)
4	Women persistently exposed to CS_2 in the viscose industry.	Reproductive hazards in women were: 1) more menstrual disorders 2) early menopausal age 3) disturbances in neuro-hormonal system, which cause the secretion of estrogens & progesterone in ovaries & diminish dehydroepiandrosterone sulfate in the adrenal gland.	Sieja *et al.* (2018)
5	Women from rayon textile & paper products jobs	Women workers of rayon textile & paper products had higher risk of spontaneous abortions (SAb); wives of men employed in transport & communication, in rayon textile, in chemical process also had a risk of SAb.	Hemminki & Niemi (1982)
6	Female spinners exposed to CS_2 in air of rayon factories (37-56 mg/m^3)	More menstrual disorder & pregnancy toxemia in exposed workers. The umbilical blood of spinner contained 5 µg/100 ml of CS_2. Milk of breast-feeding spinners have 2.8-18.6 µg/100 ml of CS_2. Exposure to higher concentration of CS_2 can affect maternal function, & CS_2 can reach into fetuses/ babies via the placenta or mother milk	Cai and Bao (1981)

SO_2- sulfur dioxide, **CS_2-** carbon disulfide, **SAb-**spontaneous abortions

The Committee noted that, carbon disulphide is classified as it 'may damage fertility or the unborn child' (35). Recently, Sieja *et al.* summarized data on female reproductive health hazards in women workers exposed to CS_2 chronically in the viscose rayon industry. They concluded that reproductive health hazards in women workers of rayon industry persistently

exposed to CS_2 are: 1) menstrual disorders were more common in exposed workers with respect to the healthy women, 2) mean menopausal age is statistically considerably earlier, compared to healthy women, 3) disorders in neurohormonal system among women workers exposed to CS_2, which cause the excretion of estrogens and progesterone in ovaries and diminish the dehydroepiandrosterone sulfate in the adrenal gland (36). Earlier, Hemminki and Niemi reported that women those were working in rayon textile and paper industries jobs had an elevated rate of spontaneous abortions; the wives of men worked in transport and communication, in rayon textile occupations, and in chemical process occupations also had an elevated rate of spontaneous abortions. While graded for age, parity, and socioeconomic status, no indication was noticed that the level of sulfur dioxide or CS_2 could be related with a threat of spontaneous abortions (37). The data available on female reproduction and occupational CS_2 exposure indicate that CS_2 exposure might affect adversely menstruation cycle and pregnancy outcome. More additional data are necessary to substantiate these reported findings with the additional studies.

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Author Contribution

Dr. Sunil Kumar conceived, compiled the data and wrote the manuscript. Dr. Anupama Sharma, Mr. Bharat Patel and Dr. Suman Choudhary collected the data and assist in finalization of MS.

Ethical Consideration

The paper does not require ethical approval.

Conflict of Interest

The authors declare no conflict of interest.

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