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Hygiene measures as primary prevention of toxoplasmosis during pregnancy: a

systematic review

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18 **ABSTRACT:**

19 Background. Hygiene measures are recommended to prevent toxoplasmosis during 20 pregnancy, although screening for seroconversion in pregnant women currently are debated 21 and practices vary among countries. 22 **Objectives:** The purpose of this systematic literature review was to assess the effectiveness of 23 hygiene measures during pregnancy to prevent toxoplasmosis infection. 24 25 Search Strategy. 26 We followed the standard MOOSE and PRISMA criteria when conducting this systematic 27 review and reporting the results. 28 29 Selection criteria. 30 A systematic literature search was conducted for studies focused on congenital toxoplasmosis 31 prevention, toxoplasmosis prevention during pregnancy, toxoplasmosis prevention and 32 hygiene measures, which were published between 1970 and August 2020, using the databases 33 of PubMed, Scope Med, EMBASE, and the Cochrane library. 34 35 **Data collection and analysis** 36 Our literature search identified 3964 articles, 3757 were excluded after review of title or 37 abstract and 67 studies were considered relevant to the subject. We reviewed risk factors for 38 toxoplasmosis infection during pregnancy and for congenital toxoplasmosis, preventive 39 measures for toxoplasmosis during pregnancy, including: dietary recommendations, pet care 40 measures, environmental measures, knowledge of risk factors and ways to control

41 toxoplasmosis infection, knowledge of risk factors for infection by health professionals,

42 knowledge of primary prevention measures by pregnant women.

43

44 **Conclusion.**

- 45 Hygiene measures are effective and applicable primary prevention to reduce toxoplasmosis
- 46 and avoid congenital toxoplasmosis and its consequences.

47 **Fundings: No**

- 48
- 49 **KEYWORDS:** Toxoplasmosis; pregnancy; primary prevention; hygiene measures

50

51

52 What's already known about this topic?

53 Hygiene measures are recommended to prevent toxoplasmosis during pregnancy, although

54 screening for seroconversion in pregnant women currently are debated and practices vary among countries.

- 55
- 56

57 What does this study add?

- 58 Hygiene measures are effective and applicable primary prevention to reduce toxoplasmosis
- 59 and avoid congenital toxoplasmosis and its consequences.

60

61 **INTRODUCTION:**

62 Systematic biological screening of toxoplasmosis in seronegative pregnant women dates back 63 to 1978 in France and is also performed in several other countries as Austria and Brazil, but it 64 is not recommended in most countries (1-4). At the end of the 1970's, toxoplasmosis 65 seroprevalence was high in women of childbearing age, but incidence of maternal infection 66 during pregnancy was so high justifying the recommendation of primary prevention. In most 67 countries including France, the prevalence and incidence of toxoplasmosis of seroconversion decreased sharply over the last 30 years. Congenital toxoplasmosis may lead to fetopathy, 68 69 hydrocephalus, and death. Most often, the disease is asymptomatic at birth, but may lead to 70 chorioretinitis that can be diagnosed only later in life. The risk of brain damage in higher in 71 case of infection in early pregnancy.

72 At the time of screening in early pregnancy, it is recommended to give written and oral 73 information to pregnant women about primary prevention. Primary prevention measures have 74 since been reaffirmed and updated on several occasions, notably in 1983 and 1996 in a 75 weekly publication of the epidemiological bulletin by the Haut Conseil de la santé publique 76 (HCSP), historically the Conseil Supérieur d'Hygiène Publique de France (CSHPF) until 2006 77 (5–7). These measures aim to reduce the incidence of toxoplasma seroconversion during 78 pregnancy in seronegative women. However, toxoplasmosis prevention management during 79 pregnancy differs between countries.

80 The purpose of this systematic review was to assess the effectiveness of hygiene measures81 during pregnancy to prevent toxoplasmosis infection.

82

83 MATERIALS AND METHODS

84 We followed the standard MOOSE and PRISMA criteria when conducting this systematic 85 review and reporting the results (8,9). A systematic literature search was conducted for 86 articles focused on congenital toxoplasmosis prevention, toxoplasmosis prevention during 87 pregnancy, toxoplasmosis prevention and hygiene measures which were published between 88 1970 and August 2020, using the databases of PubMed, Scope Med, EMBASE, and the 89 Cochrane library. Searches were performed using Medical Subject Heading terms and the free 90 keywords: ("congenital toxoplasmosis" OR "toxoplasmosis during pregnancy") AND 91 ("prevention" OR "Hygiene measures") AND ("Cohort" OR "Case-control" OR "Reviews"). 92 Furthermore, the reference lists of retrieved articles were manually scrutinized to identify 93 potential relevant studies. Two reviewers (KW and OP) independently screened the titles and 94 abstracts of the studies to identify all potential eligible studies using a predefined data 95 extraction form. Then, they independently evaluated studies for inclusion, and studies were 96 included in the systematic review if they met the following criteria: 1) cohort or case control 97 studies; 2) the risk factors of toxoplasmosis seroconversion during pregnancy; the utility of 98 hygiene measures to prevent seroconversion during pregnancy; knowledge assessment of 99 hygiene measure by health care providers and pregnant women; and assessment of hygiene 100 measures effectiveness and how they are applied and followed by pregnant women. The 101 following data were extracted: the first author's last name, year of publication, study location, 102 study design, risk factors, exposure assessment, outcome assessment, odds ratios, with their 103 confidence intervals.

Data synthesis and statistical analysis: In this review no specific statistical analysis wereperformed.

106 **RESULTS**

107 Our literature search identified 3964 articles and 3757 were excluded after review of title or
108 abstract (Figure 1). Two hundred and seven articles were further reviewed. We excluded 140
109 studies because they were considered as reporting insufficient data.

110 **Risk factors of toxoplasmosis infection during pregnancy.**

111 In 2021, Thebault *et al* published a meta-analysis of the main identified and known risk 112 factors for toxoplasmosis (10). In this meta-analysis, the quality assessment stage was passed 113 by 213 primary studies investigating risk factors for sporadic infection with Toxoplasma 114 gondii, which were conducted between 1983 and 2016 (80.5% after 2000). Excluding 115 susceptible populations other than pregnant women, and some risk factors, 187 publications 116 were retained for meta-analysis. The meta-analysis of toxoplasma sporadic infections 117 revealed the significance of transmission by environmental factors such as contact with soil 118 and contact with animals, in particular cats. The consumption of raw or undercooked meat 119 and unwashed vegetables significantly increased the odds of acquiring the disease. Shellfish 120 and raw milk were identified as significant sources of toxoplasmosis. Almost all meat 121 categories were identified as risk factors: pork, poultry, beef, processed meat, lamb, and game 122 meat. Contaminated drinking water may play a role in the acquisition of infection. Moreover, 123 the lack of hygiene in preparing food was identified as a risk factor. A significant risk factor 124 for pregnant women is traveling abroad (10).

Several limitations exist in the search for risk factors for toxoplasmosis contamination in pregnant women. Risk factor studies classify patients primarily on the basis of seroprevalence, which is an indicator of *T. gondii* infection but does not allow precise dating of the time of infection. As a result, there may be a significant time lag in studies between the collection of information on exposures of infected cases to the factors sought and the date of infection which implies a bias. This would imply that the risk factor under investigation is present consistently over time, which is not in fact the case.

132 In the meta-analysis of the ANSES (Agence nationale de sécurité sanitaire de l'alimentation, 133 de l'environnement et du travail), the authors point out that the information collected like 134 seroprevalence or food preparation are not directly comparable between them(11). The 135 serological tests to identify cases are not the same depending on the countries from which the 136 studies were conducted. Eating habits are not the same, with differences in the preparation of 137 foodstuffs whose contamination levels can vary greatly from one country to another. Among 138 the studies taken into account for the meta-analysis, only 15% of those were conducted in 139 Europe, in environments comparable to the French situation. In 2005, the Eurotoxo group 140 published a literature review of the on dietary and behavioral risk factors associated with T. 141 gondii contamination in pregnant women (12). This review included five studies carried out 142 between 1996 and 2000 in Europe, among them three case-control studies with pregnant 143 women who had a toxoplasmic seroconversion during pregnancy (13-15). The other two 144 studies were cross-sectional (16,17). The objective of these studies was to assess the 145 environmental risk factors associated with acute toxoplasmosis during pregnancy. There were some discrepancies between the studies in terms of data collection, population size, inclusion 146 147 criteria, which may explain differences in the results found in these publications. The risk 148 factors investigated were generally the same, however Bobic et al (18) and Cook et al (14) 149 did not investigate the consumption of poorly washed fruits and vegetables as a risk factor. 150 The study populations and inclusion criteria differed depending on the authors. Only the study 151 by Baril et al considered the certainty of seroconversion during pregnancy as a selection criterion (14). The date of seroconversion in the other studies was uncertain. Moreover in 152 153 2005, the French Food Safety Agency (Agence Française de Sécurité Sanitaire des Aliments -154 AFSSA -) provided a synthesis of the literature on behavioural and dietary risk factors 155 associated with T. gondii contamination (7). The AFSSA considered the five studies taken into 156 account by Eurotoxo as well as a sixth, older, cross-sectional study of Swiss pregnant women

157 carried out in 1987 and concluded the same as Eurotoxo (7). This cross-sectional study
158 included 280 women with a *T. gondii* IgG positive cord sample at delivery and 279 women
159 with an IgG negative cord sample. Overall, consumption of undercooked meat was the only
160 risk factor identified by all the studies with an Odd Ratio (OR) varying between 1.6 [95% CI:
1.2-2.1] and 11.4, p=0.00513.

162 Some risk factors are not established: Unpasteurized dairy products, shellfish, wild boar meat, 163 pork, poultry, game, are not identified as risk factors in France (18). With regards to food 164 consumption, undercooked meat, unwashed vegetables, raw milk, and shellfish are risk 165 factors only for positive Toxoplasma serology. Those results are in accordance with the 166 analysis of published outbreaks, showing that raw or undercooked meat was the origin of 167 44.7% of the outbreaks and raw vegetables of 5.3% (19)). These factors were not all sought in the questionnaire of the Baril et al. study (8, 12). Moreover, it is possible that these 168 169 differences can be explained by the cooking practices of the meats (more or less cooked) or 170 by a lesser contamination of these foods in France (farming methods). Moreover, 171 environmental exposure (gardening, farm life) is not identified in the French studies. A recent 172 study confirmed the roles of drinking water, plants, raw milk and shellfish as risk factors for 173 T.gondii contamination in pregnant women (10).

174 **Risk factors of congenital toxoplasmosis.**

Since then, in 2014, Carellos *et al* studied the risk factors associated with congenital toxoplasmosis in Brazil (20). This was a case-control study in Minas Gerais, including 175 women who had a child with congenital toxoplasmosis and 278 control women who delivered without congenital toxoplasmosis. Factors associated with a lower risk of congenital toxoplasmosis were a higher maternal age (OR = 0.89; CI 95% = 0.85-0.93), a higher level of education (OR = 0.85; CI95% = 0.78-0.92), access to drinking water (OR = 0.21; CI95% = 0.08-0.51), and housing with flush toilets (OR = 0.18; CI95% = 0.04-078). Factors associated

182 with an increased risk of congenital toxoplasmosis were the presence of cats in the vicinity 183 (OR = 2.27; CI 95% = 1.27-4.06), cat ownership (OR = 1.90; CI95% = 1.09-3.31), handling 184 of soil (OR = 2.29; CI95% = 1.32-3.96) and consumption of fresh meat that has not been 185 frozen (OR = 3.97; CI95% = 2.17-7.25). Sub-group analysis showed that water-related 186 factors (access to drinking water, flushing toilets) were significant for the rural population 187 only. The authors concluded that the risk of congenital toxoplasmosis is associated with a low 188 socioeconomic level and that maternal exposure to sources of T.gondii varies with 189 socioeconomic level. In populations with low socioeconomic levels, the main source of 190 infection could be related to oocysts with water as the main vector. These data suggest that 191 the prevention of congenital toxoplasmosis should be tailored to the reality of the target 192 population. The prevention message focuses on the known risk factors. Finally, although the 193 results of the studies included in these systematic reviews must be interpreted with caution 194 because of the methodological differences between them and their variable quality, three 195 types of dietary and behavioral factors seem to be associated with the risk of acquiring 196 toxoplasmosis in pregnant women or women of childbearing age: consumption of 197 undercooked meat, consumption of inadequately cleaned raw vegetables and poor hand 198 hygiene. These results must be carefully analyzed, because in South America, Toxoplasma 199 strains are more virulent than in Europe or in North America, so the circulating genotypes are 200 not the same (10,21,22). The clinical presentation for this strains is more severe in adults (22) 201 and we can suppose that during pregnancy, this could increase rate of contamination and 202 seroconversion in some countries.

The toxoplasmosis screening program in pregnant women differs from country to country and is a source of disagreement among scientists. France, Austria, and Slovenia have prenatal screening program(23). In France, a recent analyze of the practices have been conducted(24), because of the decreasing incidence of this infection and the cost of testing. In France, about 207 70% of pregnant women are not immune to T. gondii, and 0.2-0.25% become infected during 208 pregnancy. In case of congenital toxoplasmosis, prompt initiation of treatment reduces the 209 occurrence of cerebral signs and symptoms, as well as retinal lesions(24). Binquet and al.(23) 210 showed that prenatal screening is cost-effective as compared to neonatal screening in 211 moderate prevalence areas. In addition, prenatal screening, by providing closer follow-up of 212 women at risk increases the number of occasions for education avoiding toxoplasmosis. 213 Though most international societies do not recommend systematic screening for mainly 214 financial reasons, if congenital toxoplasmosis appears benign in France today, it is probably 215 thanks to screening and the possibility of early treatment of fetuses and/or newborns. In 216 Germany, systematic screening is not recommended, but Lange and al. (25) encourage its 217 implementation. In the United States, systematic screening is not recommended. This country 218 represents a combination of parasite and host diversity, with substantial resources for 219 management of this disease but inadequate allocation of these resources. The absence of 220 mandatory gestational screening and a fragmented healthcare system with insufficient 221 insurance coverage and access results in a poor understanding of the true scope of congenital 222 toxoplasmosis there, and financial concerns limit access to screening(26). In undeveloped 223 countries, like Marocco or Columbia, the absence of systematic screening for toxoplasmosis 224 due to a lack of means has already shown its impact(26). Screening and management of 225 congenital toxoplasmosis depends above all on public health policy and the wealth of 226 countries(26).

227 Established and recognized preventive measures of toxoplasmosis infection during228 pregnancy.

In France, where toxoplasmosis screening is mandatory, preventives measures include a number of hygiene and dietary precautions published in the weekly epidemiological bulletin by the CSHPF in 1996 (5). The *AFSSA* classifies the measures published by the *CSHPF* in

two categories: "essential measures "supported by studies with a high level of evidence and "
other measures " for which there is no scientific justification with a sufficient level of
evidence (7). They are formulated such as follows:

235 Dietary recommendations. Undercooking meat is the most widely documented risk factor in 236 the literature. The main epidemiological studies in pregnant women all conclude that there is 237 an over-risk of eating undercooked meat (13-17,27). Meat likely to contain cysts must be 238 cooked at a temperature above 67 degrees Celsius. In practice, this temperature corresponds 239 to a meat that does not allow red juice to run out when cutting. It was determined by Dubey in 240 1990 who studied the effect of temperature on the infectivity of cysts in infected pork (28). 241 Dubey was thus able to establish a thermal destruction curve estimating that a temperature of 242 67 degrees Celsius must be reached in the heart of the meat to achieve total inactivation of the 243 cysts. There is no advantage to the microwave over other cooking methods (29). Microwaves 244 were studied under experimental conditions with partial effectiveness on the infectivity of 245 T.gondii cysts at 65 degrees (41). All types of meat are susceptible to infection by T.gondii 246 and should therefore be cooked at more than 67 degrees, including venison, although beef and 247 mutton appear to be preferentially implicated in the French study by Baril et al (14). The 248 AFSSA reminds that the prevalence of toxoplasmosis is variable in cattle. It is higher in sheep 249 and leads to a high frequency of abortions in this species. In France, the contamination of 250 cattle from which meat intended for consumption comes was shown for sheep and lamb meat 251 by Halos et al in 2010 who estimated the overall seroprevalence of T.gondii was 17.7% (11.6-252 31.5%) for lambs and 89% (73.5-100%) for adult sheep (P<0.0001) (30). No significant 253 difference was observed between imported and French meats. T.gondii contamination of meat 254 was also shown for beef by Blaga et al in 2019 ((31)) who were able to estimate the level of 255 toxoplasma infection of sheep, cattle and pig meat in France, (31,32,32,33). The seroprevalence of toxoplasmosis ranged from 3% to 69.5% depending on the species and 256

257 origin of the meat. The seroprevalence increased with the age of the animals, and this 258 parameter had a significant effect on the level of seroprevalence for each species. A 259 significant difference in T. gondii infection (3% vs. 6.3%, P=0.004) was observed between 260 above-ground and free-range swine production. T.gondii contamination of French meats was 261 also demonstrated in pigs by Djokic et al in 2016 with an overall seroprevalence in pigs 262 estimated between 2 and 9%, and in wild boar by Roqueplo et al in 2017 (33,34). In the latter study, the seroprevalence of T.gondii was 16.8% among the 841 boars examined. These 263 264 observations highlight the importance of remembering that for any consumer, and particularly 265 for sensitive populations (pregnant women, immunodeficient people), the best means of 266 prevention is cooking meat thoroughly. Avoid eating marinated, smoked or grilled meat (as 267 may be the case with venison). An altenative is to freeze meat to -12°C during minimum three 268 days, which is also efficient to destroy the cysts. In France, there is no health control on 269 T.gondii, which is not routinely detected in slaughterhouses because of the complexity of 270 measuring prevalence in livestock.

271 According to AFSSA (7) in 2004, the frequency of contamination of domestic poultry could 272 represent a potential risk for humans, but parasitological data from experimental infections in 273 chicken, pigeon, duck and prevalence studies in chicken show that the parasites are mainly 274 localized in the brain, heart, to a lesser degree in other viscera and more rarely in muscles 275 (35-38). The risk of contamination is theoretically not zero but has not been assessed in 276 France. The prevalence of *T.gondii* in chickens was studied in a literature review by Dubey in 277 2010, which recalls that chickens are considered one of the most important hosts in the 278 epidemiology of *T.gondii* infection because they are an efficient source of infection for cats 279 and because humans can be infected by this parasite after eating infected chicken meat that 280 has not been properly cooked (39). The global prevalence of *T.gondii* infection in chickens is 281 very high. It has been estimated in chickens kept in backyard flocks to be close to 100%. In free-range chickens, it was estimated to be 30-50%. ANSES also proposes to control insects
that can be considered as a passive vector of oocysts (40–43).

284 The washing of raw vegetables is one of the indispensable measures according to the AFSSA, 285 whose consumption is a risk factor for T.gondii contamination, all the more so as they are 286 soiled with soil. The importance of washing raw vegetables consumed raw is recalled. An 287 additional precaution could be taken in the case of consumption of raw vegetables in restaurants outside the home (7). Regarding the detection of *T.gondii* in foodstuffs of plant 288 289 origin, there are few direct arguments for the presence of oocysts on these surfaces. Oocysts 290 have never been found in fruits and vegetables intended for human consumption. However, it 291 is known from experimental studies with mouse bioassays that oocysts can adhere to and 292 survive on fruits and vegetables for human consumption (44). The oocysts were able to 293 survive 8 weeks at 4 degrees on raspberry and blueberry berries and infect mice fed with these 294 berries. Indirectly, the transmission of *T.gondii* to humans by oocysts is demonstrated by the 295 high rate of seropositivity (between 24 and 47%) in certain vegetarian populations (45,46). 296 Finally, the consumption of raw vegetables prepared outside the home has been identified as a 297 risk factor by Baril et al (14). In the study by Kapperud et al, consumption of raw vegetables 298 or unwashed fruits was associated with an increased risk of *T.gondii* infection. As for meats, 299 there is no surveillance system for *T.gondii* in foodstuffs from vegetable origin in France. 300 Action of washing is to detaching the oocysts of the vegetables. When preparing meals: wash 301 vegetables and herbs carefully, especially if they are earthy and eaten raw. Wash kitchen 302 utensils and worktops thoroughly. Wash hands after contact with raw vegetables, fruit or meat 303 and before eating. Good hands and utensil hygiene are of major importance.

Water consumption. Water consumption as a source of contamination has been recently demonstrated in a review (47). Application of PCR for detection of *T. gondii* in water has been applied in numerous studies worldwide, and recently reviewed by Bahia-Oliveira et 307 al.(48). In Colombia, the prevalence of T. gondii DNA in 46 samples of drinking water was 308 58.6% (49). Similar prevalences were reported in raw and treated water in Bulgaria at 48% 309 (50) and in Poland at 37.5% (51). In comparison, lower prevalences of Toxoplasma in water 310 have been reported via real-time PCR in Scotland at 8.7% (N = 1411) (52), and in France's 311 Champagne-Ardenne region at 7.7% (N = 482), where some of the positive samples were 312 obtained from public drinking water(53). Humans and susceptible animal hosts can be 313 exposed to T.gondii oocysts in the environment through drinking water contaminated with 314 felid feces, but oocysts can survive various inactivation procedures especially those using 315 chemical reagents (54). For example, oocysts remain viable in water even after exposure to 316 aqueous 2% sulfuric acid for at least 18 months at 4 °C; they also resist detergents or 317 disinfectant solutions such as sodium hypochlorite. Drinking-water treatment plants using 318 chlorination as the sole method of disinfection could therefore supply water containing 319 infective oocysts (47).

320 As recommendation to pregnant women, filtered or bottled water should be consumed if 321 living or travelling in an endemic region (40). They should avoid recreating in fresh or marine 322 waters in endemic regions, or in non-endemic regions if in close proximity to overland runoff 323 from heavily populated zones. Produce should be washed with drinking water (or with filtered 324 or bottled water if living or travelling in an endemic region). Municipal and ecosystem-level 325 management strategies should be implemented to reduce the overall flux of oocysts mobilized 326 to nearshore waters through runoff. Specific recommendations include wetland preservation 327 and restoration(55), replacement of impermeable surfaces such as asphalt with alternative 328 permeable paving options(56), and storm-water treatment processes including bioswales and 329 raingardens(57). Finally, common household products such as detergents, antimicrobial 330 soaps, and bleach are not effective at killing oocysts, and their use for this purpose is not 331 recommended.

332 Pet care measures. The last indispensable measures are precautions for cats. The handling of 333 cat litter is particularly inadvisable. Cleaning should be done with boiling water and the 334 wearing of gloves is strongly recommended. It is the cats, as the definitive hosts, who ensure 335 the spread of oocysts by contaminating the environment. Overall, the prevalence in feral cats 336 appears to be higher than in domestic cats (58). In a 2018 study by Simon et al, the dynamics 337 of seroconversion of *T.gondii*, was studied in five populations of cats living in Ardennes 338 farms in France (59). Seroprevalence varied between farms, from 15% to 73%, suggesting 339 differential exposure of cats to T.gondii. On highly exposed farms, cats could be infected 340 before the age of six months. Seroconversion rates ranged from 0.42 to 0.96 seroconversions 341 per cat per year and were higher in fall and winter than in spring and summer. These results 342 suggested variations in T.gondii exposures by season and farm. Seroprevalence of T.gondii 343 was estimated at 52.7% in a 2010 study by Afonso et al. in domestic cats living in rural areas 344 in France (60): seroconversion rates varied from 0.26 to 0.39 seroconversions per cat per year. 345 In 2006, Afonso et al estimated the prevalence of *T.gondii* in an urban stray cat population at 346 18.6% between 1993 and 2004. The prevalence of T.gondii is heterogeneous depending on 347 location, environment and season. Within the same location, cats excrete oocysts only very 348 episodically. It is therefore impossible to predict the real risk associated with a cat at a given 349 time. However, epidemiological studies have identified contact with cats as a risk factor for 350 T.gondii.

To summarize, avoid direct contact with objects that could be contaminated by cat excrement (such as litter boxes, dirt) and wear gloves whenever handling these objects. Disinfect cat litter boxes with bleach is not efficient on oocysts.

Environmental measures. Hand washing is retained as an essential hygiene measure. Poor hand hygiene is associated with an increased risk of toxoplasmic contamination in the study by Baril et al (14). Contact with soil is found in the study by Cook et al. as also being

associated with an increased risk of contamination and is equated with hand hygiene as a risk
factor (13). The Afssa specifies that these measures must be extended to the hygiene of the
kitchen utensils incriminated in the work of Kapperud et al (7,15). According to the *AFSSA*meta-analysis in 2018, poor hand hygiene is associated with an increased risk of *T.gondii*contamination in pregnant women OR 1.5 (11).

362 To summarize, avoid direct contact with soil and wear gardening gloves. Wash hands after363 gardening activities even if gloves are worn.

364 These measures are based on the identification of risk factors, knowledge of the mechanisms

365 of contamination and techniques for reducing the infectious potential of cysts and oocysts.

366

367

368 Knowledge of risk factors and ways to control the infectivity of cysts or oocysts.

369 At present, it is not possible to specify the respective proportion of the different modes of 370 infection through ingestion of T.gondii due to the persistence of uncertainties about the 371 sources of contamination. The identification of risk factors for contamination has made it 372 possible to propose preventive measures and information to pregnant women or 373 immunodeficents patients who are seronegative for T.gondii. These measures would 374 theoretically have to be adapted to each pregnant woman, but each real risk cannot be 375 precisely quantified. Since it is not possible to target the risk factors for each patient and to 376 provide tailor-made information, the information has been generalized in the same way for all 377 pregnant women, regardless of their actual exposure. The relevance of these measures for 378 pregnant women was analyzed by AFSSA in 2005 in the light of the data available in the 379 literature at that time (7). The AFSSA insists on the fact that these recommendations are much 380 more concise than those sometimes found on the Internet or in various documents. It is also 381 recalled that short recommendations have a positive effect on the motivation to follow them, while too many recommendations discourage and dissuade pregnant women from making theeffort to apply them.

Recommendations in UK and Australia are the same than in France. On the other hand, American recommendations (61,62) are more strict. For example, contact with mucous membranes should be avoided when handling raw meat, gloves should be worn when handling raw meat, cats should be kept indoors, stray cats should not be handled or adopted while the woman is pregnant and cat litter box should be changed daily.

389

390 Unestablished and hypothetical preventive measures of toxoplasmosis infection during391 pregnancy.

392 Freezing the meat at a temperature of -12 degrees Celsius or lower for at least 3 days to 393 destroy the cysts. This measure is the result of Dubey's experiments on pork in 1988 (63). The 394 required freezing time depends on the thickness of the piece of meat to be inactivated. The 395 larger the piece, the longer the freezing time required to reach a potentially deep cyst. This 396 explains why industrially frozen meat can be consumed without risk, whereas domestic 397 freezing may not be sufficient to destroy the cysts. Sporulated oocysts found on plants remain 398 viable and potentially infectious after constant freezing for 28 days at -21 degrees Celsius 399 (64,65). The AFSSA also proposes measures whose effectiveness is to be further evaluated 400 (7). Among them, the consumption of marinated, salted or smoked meat could also be 401 avoided. In this regard, the consumption of dried or salted pork has been identified as a risk 402 factor by Buffolano et al OR = 2.9 [IC95%:1.6-5.5] (16). Experiments on pieces of mutton 403 meat in 1992 by Lundén et al suggest that smoking or salting procedures may be effective in 404 controlling the infective power of cysts (66). Smoking was studied by injecting a solution of 405 sodium chloride into the meat before it was smoked at a temperature not exceeding 50°C for 406 24 to 48 hours. Salting was evaluated on pieces of meat from 200 to 360 g put in plastic bags

407 with 30 to 50 g of sodium chloride and 25 to 40 g of sucrose for 64 hours at 4°C. In both 408 cases, the procedures removed the infective power of *T.gondii* cysts. However, the authors 409 pointed out that the exact mechanism of efficacy on the infectivity of the cysts is poorly 410 known and could be related to the changes in osmotic pressure associated with the addition of 411 salt and sugar in meat. Moreover, recent study (67) confirm the safety of ready to eat 412 products containing pork with respect to T. gondii prepared using typical NaCl concentrations 413 at or above 1.3%, and industry standard fermentation and drying procedures.

414 Among the preventive measures are cited the consumption of seafood although no T.gondii 415 infection linked to seafood consumption has yet been found in France, ANSES states in 2018 416 that shellfish (oysters and mussels) have been identified as a risk factor for contamination in 417 two meta-analysis (10,68). The presence and survival of oocysts in shellfish and other 418 foodstuffs from the sea are suspected by indirect arguments such as the existence of cases of 419 marine mammals infected with T.gondii (69-71). More recently, in 2017, a Chinese study 420 revealed the presence of T. gondi oocysts in oysters sold in a market in China (72). A total of 421 26 of the 998 oysters tested tested positive by PCR amplification (2.61%). This study suggests 422 that oysters have the ability to filter and retain oocysts in their tissues. Another 2014 Chinese 423 study of 3432 shellfish showed low (N=5/3432) but not zero contamination of T.gondii in 424 these species (73). In a New Zealand study in 2018, T.gondii contamination in the form of 425 sporulated oocysts was detected in 16.4% (N=13) of a sample of 104 commercial mussels 426 (74). In the 2018 meta-analysis, ANSES concludes that seafood consumption is associated 427 with an increased risk of *T.gondii* in the general population (10,11). Seafood should be 428 thoroughly cooked to inactivate oocysts.

The consumption of raw goat's milk was also one of the measures whose effectiveness needed to be further evaluated. The *ANSES* recalled that it had been the cause of some cases of toxoplasmosis and reasonably advocated avoiding it. In the meta-analysis of 2018, the 432 identification of raw milk as a risk factor was based on 16 publications for the general
433 population and 27 in pregnant women. In 2017, a literature review by Boughattas on milk
434 consumption and toxoplasma infection reported, despite heterogeneous data, that the main
435 source of infection was goat's milk (75).

Although developed from a scientific substrate, these measures to prevent toxoplasmic infection can only be effective if they are properly followed. In order to do so, they must be well disseminated to health professionals caring for women of childbearing age outside and during pregnancy. It is also necessary to evaluate the knowledge of pregnant women informed by these professionals and the impact of these measures on women's behaviour. Moreover, the psychological and dietary impact of the implementation of primary prevention measures in pregnant women is not evaluated in the literature.

443 Knowledge of primary prevention measures by health professionnals.

444 Several studies around the world have assessed praticians' knowledge, attitudes, and practices 445 regarding prevention of infections in pregnancy. In 2009 in United States(76), among 305 446 gynecologists interviewed, about 84% reported counseling pregnant women about preventing 447 infection from T.gondii. The majority reported time constraints were a barrier to counseling, 448 although most reported educational materials would be helpful. In 2012, Sellier et al studied 449 the knowledge and practices of midwives on the primary prevention of maternal toxoplasmic 450 infections during pregnancy in France(77). This was a survey of 139 midwives working in 451 the public, private or liberal sectors in the Rhône-Alpes region, by means of a questionnaire. 452 The midwives had satisfactory theoretical knowledge of toxoplasmosis with between 76.5% 453 and 100% correct answers depending on the items for 102 participants. However, 49% forgot 454 to recommend good hand hygiene, 38% did not adapt the advice given to the profile of their 455 patients and 62% did not repeat the advice at the end of pregnancy. There is little other work 456 on the subject. We have data from general practitioners in Burgundy in a work by Binquet 457 which highlighted a poor level of knowledge of the modes of contamination by these 458 doctors(78). Nevertheless, it was an anonymous survey with a low response rate of only 25% 459 with no comparison between participants and non-participants making it difficult to interpret 460 the results. Elsewhere in the world, there are cross-sectional studies conducted in the United 461 States in 1999 and 2005, with an update in 2012, which highlight the limits of health 462 professionals' knowledge in this field(79,80). The study by Kravetz and Federman included a 463 random sample of 49 obstetricians, 40 internists and 13 family doctors, and highlighted in 464 particular the poor prioritization of risk factors for contamination by practitioners and their 465 overestimation of the weight of contact with cats(79). The authors concluded that there was a 466 need for more information to be provided to health professionals, especially family doctors 467 and internists. The Jones et al. study was updated in 2015(81). It consisted of a questionnaire 468 sent to 1056 members of the American College of Obstetricians and Gynecologists (ACOG). 469 The results showed a minimum of correct answers between 19.7% and 40.3% depending on 470 whether or not the members included in the study were members of the Collaborative 471 Ambulatory Research Network (CARN). Of the participants, 80.2% had not diagnosed any 472 acute maternal T.gondii infection in the past 5 years. Among them, 12.7% had correctly 473 identified the screening role of IgG avidity testing, 42.6% had performed serological 474 screening for T. gondii in some asymptomatic pregnant women, and 62.1% had used 475 appropriate approaches. Health care professionals in the northeastern United States were 2.02 476 times more likely to perform routine screening than those in the West (p = 0.025). Female 477 physicians were 1.48 times more likely than male physicians (p = 0.047) to offer routine 478 screening. Participants felt that updating the ACOG recommendations on the screening and 479 management of acute *T.gondii* infection in pregnancy was useful. In 2011, a Brazilian study 480 by da Silva et al looked at health professionals' knowledge of risk factors(82). In Brazil, an 481 endemic region, the prevention of congenital toxoplasmosis most often relies on serological 482 screening of pregnant women. According to the authors, many cases could be prevented by 483 simple precautions during pregnancy. The objective of this study was to assess knowledge 484 about toxoplasmosis among professionals working in prenatal care in this high-prevalence 485 region, a questionnaire was administered to 118 nurses and physicians. It included questions 486 on diagnosis, clinic and prevention. Regarding prevention, 97.4% of professionals agreed that 487 cats are the animal that eliminates the parasite in the stool, but 51.7% said that dogs also 488 eliminate oocysts. The greatest number of errors was highlighted in relation to the education 489 of non-immune pregnant women in relation to raw vegetables with only 5.2% of correct 490 answers.

491 Knowledge of primary prevention measures by pregnant women.

492 In France there are four dating from the 1990s cited in the AFSSA and HAS reports which 493 evaluated the levels of knowledge by pregnant women of measures to prevent toxoplasmosis 494 during pregnancy(83,84). Pregnant women's knowledge levels were considered satisfactory 495 in three of these studies because between 71% and 96% of the women included could cite two 496 means of preventing toxoplasmosis(14,85,86). In the fourth study, less than half of the women 497 included could cite two ways to prevent toxoplasmosis(87). In two studies, seronegative 498 women were better informed than immunized women(14,86). In a third study, no difference 499 in knowledge was found between seronegative women and immunized women(87). The 500 fourth study did not specify the knowledge in seropositive patients for T.gondii(85). The 501 heterogeneity of the results can be partly explained by methodological differences: for 502 example, in the study by Baril et al(14), the pregnant women interviewed were all 503 seronegative in early pregnancy, which was not the case in the other three studies, which 504 therefore included women who were seropositive in early pregnancy and therefore may not 505 have had any recall of information on toxoplasmosis. The questionnaires were not completed

in the same way depending on the study (by telephone or face-to-face). The questions askedwere different or differently worded, which could lead to different responses from patients.

508 Elsewhere in the world, a U.S. study was conducted in 2002 with pregnant women who were 509 interviewed to determine their knowledge about toxoplasmosis and their infection control 510 practices. Volunteer obstetricians from the American College of Obstetricians and 511 Gynecologists recruited the 403 participants who completed the questionnaire(88). Among 512 these women, 48% had indicated that they had received information about toxoplasmosis; 513 however, only 7% knew that they had been tested for this disease. Forty percent of the women 514 surveyed knew that toxoplasmosis is caused by an infection, but 21% thought a poison was 515 the cause. The highest level of knowledge was about the role of cats in toxoplasmosis; 61 516 percent of participants responded that the parasite is excreted in the feces of infected cats and 517 60 percent responded that people could become infected by changing the cat litter. The level 518 of knowledge about other risk factors was low; only 30% of the women knew that T.gondii 519 can be found in raw or undercooked meat. The level of knowledge about modes of 520 contamination was associated with education, age and ethnicity. Nevertheless, a high 521 percentage of women reported that they did not eat undercooked meat during pregnancy and 522 that they used good hygienic measures, such as washing their hands after handling raw meat, 523 gardening or changing cat litter. The authors concluded that, with the exception of the risk of 524 transmission by cats, the knowledge of pregnant women about toxoplasmosis was low. 525 However, toxoplasmosis prevention practices appeared to be generally good.

526 Implementation of primary prevention measures by pregnant women.

527 Preventive measures can only be effective if healthcare professionals are aware of the risk 528 factors and the advice to be given to pregnant women. Pregnant women must then be well 529 informed and aware of these preventive measures, which mean that this knowledge must have 530 an impact on the behaviour of pregnant women. In France, only one study (1994) cited in the 531 AFSSA report evaluated the degree of application of measures to prevent toxoplasmosis by 532 seronegative pregnant women at the beginning of pregnancy(83). The results were poor, with 533 only 17 per cent of pregnant women having satisfactorily implemented preventive measures. 534 No significant association was found between the degree of implementation of preventive 535 measures and age, parity or socio-professional category. On the other hand, preventive 536 behaviors were associated with women's level of knowledge.

537 Health education programs are what works.

538 In 2008 a review of the literature by the Eurotoxo group attempted to answer the question of 539 the effectiveness of measures or programs for the primary prevention of T.gondii infections in 540 pregnant women(89). A total of four studies and two unpublished works met the inclusion 541 criteria. All studies had methodological shortcomings. The first, a Belgian study, supported a 542 significant decrease in the incidence of seroconversion to T.gondii after the introduction of 543 intensive information on toxoplasmosis among selected pregnant women(90). The second 544 study was Polish and concluded in favour of a significant increase in knowledge after the 545 implementation of a multi-faceted public health education program(91). The third study was 546 Canadian and supported increased knowledge and behaviour change in the group that 547 received specific information compared to the control group(92). The last study was French 548 and did not show any significant change in risk behaviours as a result of information provided 549 by a doctor(93). This review highlighted the weakness of the literature in this area and the 550 lack of studies measuring actual seroconversion. There was only suggestive evidence that 551 health education approaches could help reduce the risk of congenital toxoplasmosis, but this 552 problem already required further study using a more rigorous methodology and research 553 design. Among the unpublished works, the Risk Assessment, Information, Awareness, 554 randomized controlled trial evaluated the effect of a prenatal toxoplasmosis education 555 program on the incidence of seroconversions during pregnancy, the level of knowledge,

preventive attitudes and behaviors of pregnant women, and the impact of a prenatal 556 557 toxoplasmosis education program on the incidence of seroconversions during pregnancy(94). 558 It was a multi-centre project carried out between 1994 and 1995 in seven departments of the 559 Rhône-Alpes region. A total of 5,023 seronegative pregnant women had been recruited in the 560 first trimester of their pregnancy by general practitioners and obstetric gynaecologists. These 561 women were randomized into groups. The first group consisted of 3,268 pregnant women 562 who had received information through an educational audiovisual support providing specific 563 information on toxoplasmosis in addition to the information usually provided. The other 564 group consisted of 1755 pregnant women who had received the usual information. The low 565 incidence of seroconversions during pregnancy in both groups (13/2,591 in the intervention 566 group and 4/1,358 in the control group; p=0.35) did not reveal any significant difference 567 according to the level of information the pregnant women had received about the risk factors 568 for *T.gondii* contamination. The seroconversion rates for toxoplasmosis detected during the 569 study did not differ between groups (RR = 1.70; 95% CI = 0.56 to 5.21; N = 3949). 570 Concerning the study of behavioral changes in the two groups of women, the statistical 571 analysis only took into account the women who had completed the study questionnaires, 572 which were 1953 (60%) women in the first group and 837 women (48%) in the second group. 573 At inclusion, 92% of the pregnant women knew the risk of infection associated with eating 574 undercooked beef, 90% knew the risk associated with eating poorly washed salad and 82% 575 knew the risk associated with handling cat litter. On the other hand, only 55% of women were 576 aware of the prevention of hand washing after handling raw meat. In addition, 88% of women 577 reported washing vegetables and fruit intended to be eaten raw. However, of the 97% who 578 had eaten meat at least once, only 55% had always eaten it well cooked. Overall, there was a 579 significant but small improvement in women's level of knowledge about toxoplasmosis and 580 its prevention among those patients who had been informed and who had a good knowledge 581 of the disease at inclusion in the study as well as a level of education above the baccalaureate 582 level. However, no association was found between preventive measure behaviors and group 583 assignment (information vs. no information). There were no significant differences in 584 behaviors related to cooking meat (OR = 1.21; 95% CI = 0.98-1.50) or hand washing (OR = 585 1.01; 95% CI = 0.83-1.22). Differences in behaviors were associated with the level of 586 knowledge and attitudes toward prevention at inclusion. Since 2009, Di Mario et al have been 587 trying to answer the question of the effectiveness of prenatal education to prevent congenital 588 toxoplasmosis through a review of the literature conducted by the Cochrane Database(95). 589 Only randomized or quasi-randomized controlled trials evaluating any type of prenatal 590 educational intervention for *T.gondii* infection during pregnancy and how to avoid it could be 591 included and considered in this meta-analysis. The authors note that when the protocol for this 592 systematic review was first published in 2006, no other systematic review on the effectiveness 593 of prenatal education for the congenital prevention of toxoplasmosis was available. They 594 specify that of the six studies considered in the literature review by Gollub et al in 2008, only 595 two were randomized controlled trials (Carter 1989; Wallon 2006), the other trials being 596 observational studies (Breugelmans 2004; Foulon 2000; Nguyen 2004; Pawlowski 2001). The 597 authors did not provide a meta-analysis of the data due to the lack of standardization in the 598 reporting of results. The first study was already included in the 2008 review and compared 599 two randomly assigned groups of women, which is why it was also included in Di Mario's 600 meta-analysis(92). The study was conducted in Ontario, Canada, and involved 432 pregnant 601 women who had attended early prenatal classes in six centres. It was a cluster randomized 602 trial. In this study, 26 groups were randomized to attend a 10-minute presentation on 603 toxoplasmosis prevention during the first prenatal education class. The remaining 26 groups 604 were randomized not to receive this information during the prenatal education class. Pre- and 605 post-training questionnaires were conducted. Among the informed patients, the following 606 changes were observed. Change in pet hygiene behaviors: informed women performed 607 significantly better than uninformed women (p < 0.05); Change in food hygiene behaviors: 608 informed women performed significantly better than uninformed women with respect to 609 cooking roast beef (p < 0.05) and hamburgers (p < 0.01); other items were already good in the 610 pre-test. In terms of personal hygiene, informed women behaved significantly better than 611 others only in the sub-group of women who were not unemployed (p < 0.05). Only 5% of 612 women in the intervention group recalled that they had received specific information on 613 toxoplasmosis prevention in prenatal classes. The authors concluded that prenatal education 614 can help to change the behavior of pregnant women, including personal, food and pet-related 615 hygiene. There were no results on the incidence of toxoplasmosis by group. The meta-616 analysis of Di Mario et al. also includes the results of the Risk Assessment, Information, 617 Awareness, randomized controlled trial using data presented by Wallon et al. in 2006(96). 618 Overall, current data do not demonstrate the effectiveness of primary prevention measures for 619 congenital toxoplasmosis on the incidence of the disease. The results are only in favor of an 620 effect on the behavior of pregnant women with regard to preventive measures. Further well-621 conducted studies are needed to substantiate the question, but this work is costly and 622 technically difficult to implement (number of subjects to be included, strong decreasing 623 incidence of the disease...).

624

625 Conclusion.

With current epidemiological data, it has been possible to identify a proven number of riskfactors for food and behavioral contamination relevant to each country worldwide situation

628 1/Consumption of meat, especially if it is undercooked;

629 2/Consumption of vegetables;

630 3/Contact with cats;

631 4/Contact with the soil (especially through gardening).

In addition to the already known risk factors for transmission of congenital toxoplasmosis,
this systematic review described evidence for the transmission way of toxoplasmosis by
shellfish, and drinking water. Raw milk (goat/cows) and game meat are also highly suspected
to have this role.

There is not a high level of evidence that demonstrate that the implementation of prevention
measures reduces the incidence of seroconversions in pregnant women. However, it seems
reasonable to avoid known risk factors.

639 Compliance with these preventive measures requires that health professionals must give the 640 information to pregnant women in a clear manner. This implies that health professionals must 641 be fully trained on toxoplasmosis, and the known risk factors for contamination. The 642 information provision must be well-organized during prenatal care visits. A recent opinion of 643 expert panel of French experts on toxoplasmosis including gynecologists, pediatricians and 644 parasitologists still recommend pursuing the screening program for prevention of congenital 645 toxoplasmosis. Hygiene measures and pregnancy screening program represent the two main 646 primary prevention tools to avoid congenital toxoplasmosis and its consequences.

Figure 1. Flow diagram of study selection process.



Authors contribution:

- 653 All persons listed as authors have contributed substantially to the design, performance,
- 654 analysis, and reporting of this work.
- **KW**, **ML**, **IV**, **LM**, **OP**: collected data, analyzed data, wrote paper.
- **KW**, **LP**, **JS**, **OP**: Designed study, analyzed data, wrote paper.

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