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Effects of maternal modafinil treatment on fetal development and neonatal growth parameters — a multicenter case series of the European Network of Teratology Information Services (ENITS)

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Abstract

Objective: In recent years, safety concerns about modafinil exposure during pregnancy have emerged. In particular, increased risks for major congenital anomalies (MCA) and impaired fetal growth were reported, although study results were conflicting. Our investigation aims to examine previously reported safety signals.

Method: Multicenter case series based on data from 18 Teratology Information Services from 12 countries. Modafinil exposed pregnancies with an estimated date of birth before August 2019 were included in this study. For prospectively ascertained pregnancies, cumulative incidences of pregnancy outcomes, rate of nonchromosomal MCA in first trimester exposed pregnancies and percentiles of neonatal/infant weight and head circumference (HC) were calculated. Potential dose-dependent effects on fetal growth were explored by linear regression models. Retrospectively ascertained cases were screened for pattern of MCA and other adverse events.

Results: One hundred and seventy-five prospectively ascertained cases were included, of which 173 were exposed at least during the first trimester.

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For affiliations refer to page 11

Cumulative incidences for live birth, spontaneous abortion and elective termination of pregnancy were 76.9% (95% CI, 68.0%–84.8%), 9.3% (95% CI, 5.0%–16.9%), and 13.9% (95% CI, 8.1%–23.1%), respectively. Nonchromosomal MCA was present in 3/150 live births, corresponding to an MCA rate of 2.0% (95% CI, 0.6%–6.1%), none were reported in pregnancy losses. Compared to reference standards, birth weight (BW) tended to be lower and neonatal HC to be smaller in exposed newborns (data available for 144 and 73 of 153 live births, respectively). In nonadjusted linear regression models, each 100 mg increase of average dosage per pregnancy day was associated with a decrease in standard deviation score (SDS) of −0.28 SDS (95% CI, −0.45 to −0.10) for BW and of −0.28 SDS (95% CI, −0.56 to 0.01) for HC. Screening of 22 retrospectively reported cases did not reveal any specific pattern of MCA or other adverse outcomes.

Conclusion: The results do not indicate an increased risk of MCA after in utero exposure to modafinil, but a tendency toward lower BW and reduced neonatal HC. However, these findings should be regarded as preliminary. Until further studies allow for a definite conclusion, modafinil should not be used during pregnancy.

KEYWORDS

"congenital abnormalities" [MeSH], "drug-related side effects and adverse reactions" [MeSH], "growth and development" [MeSH], "modafinil" [MeSH], "pregnancy" [MeSH]

1 | INTRODUCTION

Modafinil and its R-enantiomer armodafinil (used interchangeably in the following manuscript as modafinil) are psychostimulants enhancing alertness and cognitive functions. Their mode of action is not fully understood, but includes modulation of various neuronal pathways. Although the *European Medicines Agency* (*EMA*) restricted approval to narcolepsy, modafinil is used for a variety of conditions associated with excessive daytime sleepiness and fatigue. In addition, modafinil is sometimes prescribed for psychiatric conditions[1,2] such as bipolar and substance use disorders, and there is misuse by healthy people, mostly for cognitive enhancement.[3,4] Usual daily modafinil dosages range from 200 to 400 mg.

Safety concerns about modafinil exposure during pregnancy first emerged in 2019. Evaluation of the manufacturer's US pregnancy registry and other post-marketing data indicated various risks for embryos/fetuses and newborns after modafinil exposure during pregnancy, especially an increased risk for major congenital anomalies (MCA). As a result, the *EMA* and *Health Canada* issued direct health care professional communications, warning against the use of modafinil during pregnancy. However, underlying data were not publicly accessible and observed unfavorable effects were reported inconsistently: *Health Canada* reported a high rate of MCA (17.3%) among the exposed fetuses (cardiac defects: 4%) as well as pregnancies ending in spontaneous abortion (SAB) and cases with intrauterine growth restriction, neonatal microcephaly and poor physical development after birth.[5] Other communications[6,7] did not mention any impairment of fetal or neonatal growth, but also described an MCA rate of 15% (including cardiac defects, hypospadias, and orofacial clefts).

When these signals emerged, no other informative clinical data on the safety of modafinil during pregnancy were available.[8,9] Animal studies indicated embryotoxicity but no teratogenicity.[10] After warnings by health authorities, further data on the risk of congenital malformation, also based on a limited number of patients, were published in quick succession and provided conflicting results. Kaplan et al.[11] conducted a further analysis from the previously mentioned US pregnancy registry established by the manufacturer. MCA were identified in 13 out of 97 prospectively evaluated live births after first trimester exposure to modafinil, resulting in an MCA rate of 13%. However, abnormalities included both minor (torticollis) and major (hypospadias and heart defects) congenital anomalies. The SAB rate was 11%. Damkier and Broe[12] analyzed data from the Danish national health registries to assess the MCA risk after first trimester exposure to modafinil. Six out of 49 modafinil exposed

pregnancies resulted in a fetus/infant with MCA (type not specified), corresponding to an MCA rate of 12%. The comparison to a cohort of nonexposed fetuses/infants yielded an adjusted odds ratio (aOR) of 2.7 (95% CI, 1.1–6.9). These aforementioned findings stand in contrast to the results of Cesta and colleagues,[13] based on Swedish and Norwegian health registries: An MCA was identified in 3/133 live births with first trimester exposure to modafinil, corresponding to a 2.3% MCA rate and a crude risk ratio of 1.06 (95% CI, 0.35–3.25) compared to nonexposed infants.

The limited and contradictory data published to date are insufficient for a reliable risk assessment of pregnancy outcome after modafinil exposure.[14] This is particularly true for the risks of fetal growth restriction, microcephaly and poor physical development ("failure to thrive"). Our multicenter case series includes the largest number of modafinil exposed pregnancies so far, and it aims to investigate all relevant safety signals that were previously reported with modafinil use during pregnancy.

Significant outcomes

- The rate of 2.0% (3/150) major congenital anomalies in the prospective cohort of first trimester modafinil exposed pregnancies does not indicate an increased risk.
- Our analysis suggests an inhibiting effect of modafinil on fetal growth, but these findings are preliminary and their clinical relevance is unknown.
- Until safety concerns from this and other studies are more extensively investigated, patients should avoid modafinil intake during pregnancy.

Limitations

- Even though this multicenter case series covers the largest number of exposed pregnancies published so far, modafinil cohort size is still limited.
- The validity of the results on growth effects might be impaired by the heterogeneity of contributing countries and reference charts.
- Results are not adjusted for potential confounding factors. Unmeasured confounding and/or confounding by indication might be at least partly responsible for the observed effects on fetal growth.

2 | MATERIAL AND METHODS

2.1 | Data collection and ascertainment of cases

Eighteen Teratology Information Services (TIS) from 12 countries contributed to the data (Table S1). TIS collaborate in the *European Network of Teratology Information Services* (*ENTIS*, www.entis-org.eu) and/or the North American *Organization of Teratology Information Specialists* (*OTIS*, www.mothertobaby.org/about-otis/). They offer risk assessment of medication and other exposures during pregnancy on request of individual health care professionals and/or patients. Enrolment of patients was similar across participating centers, using structured telephone interviews and/or mailed questionnaires for the collection of data on maternal and neonatal characteristics, pregnancy outcome, birth defects, gestational age at delivery, and pediatric findings. Follow-up period including time for plausibility check and completion of missing data varied between participating centers. Therefore, a period of 7 months was set between the cut-off for the estimated date of birth (EDOB) of included pregnancies and the deadline for submitting modafinil exposed cases. Maternal characteristics included age, body mass index (BMI), comorbidities, concomitant medication, and pregnancy complications, among others. In cases with missing values of noncrucial variables (see exclusion criteria), analysis was limited to the available data. For each variable, the number of informative cases is presented in the respective Tables and Figures.

Cases were considered prospective, when pregnancy outcome was unknown and no prenatal pathology was diagnosed at the time of first contact. Otherwise, cases were labeled as retrospective. Rates or percentages were only calculated for prospectively ascertained cases. Since adverse outcomes are known to be overrepresented in retrospective reports, retrospectively ascertained cases were reviewed separately in order to screen for pattern of congenital malformations or other adverse outcomes.

All participating centers obtained the study protocol in advance and ethics committee approval was obtained as required for each participating center.

2.2 | Exposure and inclusion criteria

All exposed pregnancies with an EDOB before August 2019, and information on pregnancy and neonatal outcome were included in the analysis. Pregnancies were defined as exposed in case of any exposure to modafinil between 2 + 0 weeks after last menstrual period and delivery. First trimester exposure was defined as any exposure from gestational weeks (GWs) 2 + 0 to 12 + 6.

Exposure patterns were evaluated descriptively. Centers were contacted in cases where crucial data like information on exposure and/or pregnancy outcome were missing and subsequently excluded from the analysis if no additional data could be obtained. Teratogenic or fetotoxic co-medication was not an exclusion criterion but was considered for assessment.

2.3 | Pregnancy outcome

Cumulative incidences were calculated for the different pregnancy outcomes: live birth, SAB, that is, pregnancy loss with BW < 500 g or gestational age <24 completed weeks, ETOP (elective termination of pregnancy) and stillborn. For estimating the probability of SAB while avoiding bias due to delayed study entry and accounting for competing risks, cumulative incidences and 95% confidence intervals (CI) were calculated using the Aalen–Johansen estimator. For this purpose, ETOP and live births were considered competing events.[15] To avoid immortal time bias,[16] pregnancies with start of modafinil exposure after study entry were excluded from this particular analysis.

2.4 | Major congenital anomalies

MCA rates were calculated for fetuses and infants with first trimester exposure to modafinil. For this purpose, the number of infants and fetuses with known MCA was divided by the number of all live born infants plus the number of all pregnancy losses with known MCA. Infants or fetuses with reported chromosomal disorders were excluded from the calculation of MCA rates. Classification of MCA was based on the standards of the *European network of population-based registries for the epidemiological surveillance of congenital anomalies* (*EUROCAT, Guide 1.4 and reference documents*, see also www.eurocat-network.eu). Accordingly, a severe microcephaly would be classified as MCA, if neonatal head circumference (HC) was less than −3 SD, whether by country-specific or by international reference charts.

2.5 | Neonatal growth parameters

BW and neonatal HC were evaluated according to gestational age and neonatal sex. Percentile values and standard deviation scores (SDS) were derived from country-specific reference standards (if available) or international reference standards. Details are stated in Table S2. In our study cohort, SDS means of growth parameters according to country-specific reference standards differed markedly from those according to international reference standards (Table S3), as has already been shown for other data sets.[17] Therefore, SDS were based on country-specific reference standards wherever possible to ensure for each modafinil exposed newborn the most appropriate reference population.

2.6 | Potential dose-dependent effects on fetal growth

A potential dose-dependent effect of modafinil on BW and HC was explored by linear regression models. We correlated SDS of BW and HC for each newborn to her/his mother's cumulative modafinil dosage (in mg) throughout pregnancy. To take into account the different durations of gestation, each cumulative dosage was divided by duration of pregnancy, resulting in the average dosage per pregnancy day (in mg/day). In addition to the aggregate analysis, we stratified by country; countries contributing less than 10 cases to the analysis were evaluated combined. Due to the limited sample size and the number of missing covariates, we did not adjust for covariates such as maternal age, parity, BMI or treatment indication.

2.7 | Postnatal growth

To explore potential effects of long-term prenatal modafinil exposure on postnatal infant growth ("failure to thrive"), we determined SDS for postnatal measurements of weight and HC in live-born infants, if the following conditions were met: (a) long-term exposure to modafinil in utero, that is, exposure in all three trimesters and (b) at least one measurement of growth parameters after the first month of life. If available, country-specific reference charts were used,[18] otherwise international charts provided by the World Health Organization (WHO, for Australian and US data).[19]

Statistical analyses were conducted using R version 4.1.1.[20]

3 | RESULTS

Eighteen participating centers submitted data on 209 cases with in utero exposure to modafinil, of which 175 were ascertained prospectively and 22 retrospectively. Twelve cases were excluded from the study, because they were duplicates, did not meet inclusion criteria, or lacked crucial data. For further information, see Table S1. For each of the defined outcome parameters, the number of

analyzed cases and the respective inclusion criteria are summarized in Table S4.

3.1 | Maternal characteristics

Maternal characteristics are shown in Table 1. A substantial proportion of patients (37.5%) were overweight or obese; 1.7% were affected by pre-existing diabetes mellitus and 7.7% by gestational diabetes. Furthermore, relevant comorbidities with concurrent medication as well as nicotine and alcohol consumption were frequent. The indication for modafinil treatment was narcolepsy in the majority of patients (63.9%, $N = 106/166$). Median of maternal modafinil dosage was 200 mg (interquartile range 100–300 mg).

3.2 | Exposure patterns

Most women ($N = 166/175$) started modafinil intake before pregnancy and the majority discontinued modafinil during the first trimester ($N = 102/175$). 98.9% of all pregnancies ($N = 173/175$) were exposed during the first trimester, only 23.4% during all trimesters ($N = 41/175$). A total of 171/175 pregnancies were exposed to modafinil, 4/175 to armodafinil. In narcolepsy patients, the mean average modafinil dosage per day was higher than for other indications (248 vs. 187 mg/d), while relevant comorbidities were less frequent (33.0% vs. 58.3%). For further details of exposure patterns, see Figure 1.

3.3 | Pregnancy outcomes

Of the 175 prospectively recorded pregnancies, 152 resulted in 153 live born infants (one set of twins) and 10 in SAB. Thirteen resulted in ETOP, none with reported MCA. The estimated cumulative incidences for live births, SABs and ETOPs were 76.9% (95% CI, 68.0%–84.8%), 9.3% (95% CI, 5.0%–16.9%), and 13.9% (95% CI, 8.1%–23.1%), respectively. Two pregnancies resulting in live births were excluded from this analysis because modafinil exposure started after study entry. For further details of pregnancy outcome, see Figure 2.

3.4 | Major congenital anomalies

Of the 173 prospectively ascertained pregnancies with first trimester exposure to modafinil, 150 pregnancies

TABLE 1 Maternal characteristics (prospectively ascertained cases).

Maternal age ($N = 168$)[a]: mean; median (IQR), (min/max)	3fe1.6; 32 (28–35), (20/44)
Maternal BMI[b] ($N = 80$)[a]: mean; median (IQR), (min/max)	24.7; 23.7 (21–27.6), (17/39.2)
Maternal BMI ≥ 25	37.5% ($N = 30/80$)
Maternal BMI ≥ 30	16.3% ($N = 13/80$)
Maternal smoking[c] ($N = 126$)[a]	23.0% ($N = 29/126$)
Maternal alcohol consumption[c] ($N = 123$)[a]	13.8% ($N = 17/123$)
GW[d] **at 1st TIS contact**[e] ($N = 175$)[a]: mean; median (IQR)	11.2, 8 + 3, (6 + 2 − 14 + 1)
Treatment indication for modafinil ($N = 166$)[a]	
Narcolepsy	63.9% ($N = 106/166$)
Other sleep disorder; including hypersomnia	20.5% ($N = 34/166$)
Multiple sclerosis (MS)/fatigue in MS	6.6% ($N = 11/166$)
Other neuropsychiatric disorder	9.0% ($N = 15/166$)
Average daily modafinil dosage in mg ($N = 146$)[a]: mean; median (IQR), (min/max)	229; 200 (100–300), (19/700)
Average daily modafinil dosage per pregnancy day[f] **in mg** ($N = 144$)[a]: mean; median (IQR), (min/max)	110; 65 (28–150), (0.2/604)
Relevant comorbidities	41.3% ($N = 71/172$)
Psychiatric and neurological disorders ($N = 172$)[a]	34.9% ($N = 60/172$)
Preexisting diabetes mellitus ($N = 172$)[a]	1.7% ($N = 3/172$)
Gestational diabetes mellitus ($N = 142$)[a]	7.7% ($N = 11/142$)
Other comorbidities ($N = 172$)[a]	16.3% ($N = 28/172$)
Relevant concurrent medication ($N = 173$)[a]	
Any relevant concurrent medication[g]	62.4% ($N = 108/173$)
Teratogenic medication during 1st trimester[h]	2.9% ($N = 5/173$)
Psychopharmacological medication[i]	46.8% ($N = 81/173$)
Two or more psychotropic drugs	17.3% ($N = 30/173$)
Immune modulating medication[i]	8.1% ($N = 14/173$)

[a]Study cases with sufficient information for analysis.
[b]Body mass index.
[c]Any reported exposure during pregnancy.
[d]Gestational week.
[e]Teratology Information Services.
[f]Cumulative dosage divided by the duration of pregnancy in days.
[g]Any drug exposure, regardless of the trimester of pregnancy, was considered relevant, except common drugstore products, homeopathics and so forth.
[h]Teratogenic co-medications were valproate (2 patients), carbamazepine, warfarin and lithium.
[i]Any exposure, regardless of the trimester of pregnancy, was considered relevant.

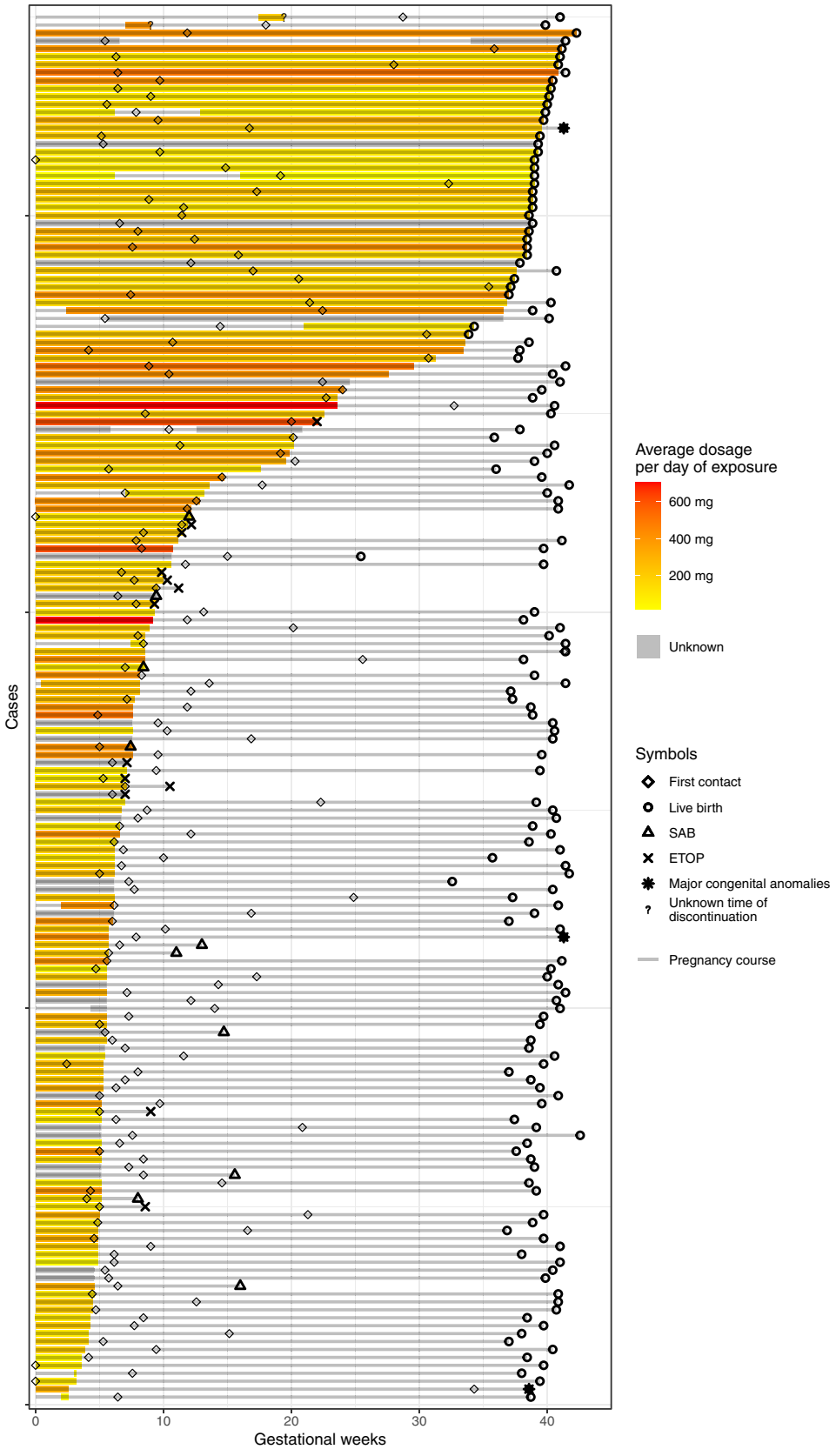

FIGURE 1 Modafinil exposure patterns and pregnancy outcomes. The horizontal lines represent the courses of individual pregnancies ($N = 175$). The colored bars mark exposure intervals and average dosage per day of exposure. For calculating the average dosage per day of exposure, we divided the cumulative dosage in pregnancy (mg) by the duration of exposure (days).

resulted in 151 live born children. Two cases were excluded from the calculation of MCA rates because of chromosomal disorders: one spontaneously aborted fetus was diagnosed with trisomy 21 (and an atrioventricular septal defect accompanied by hydrops fetalis) in GW 14, and one live-born infant was diagnosed with trisomy

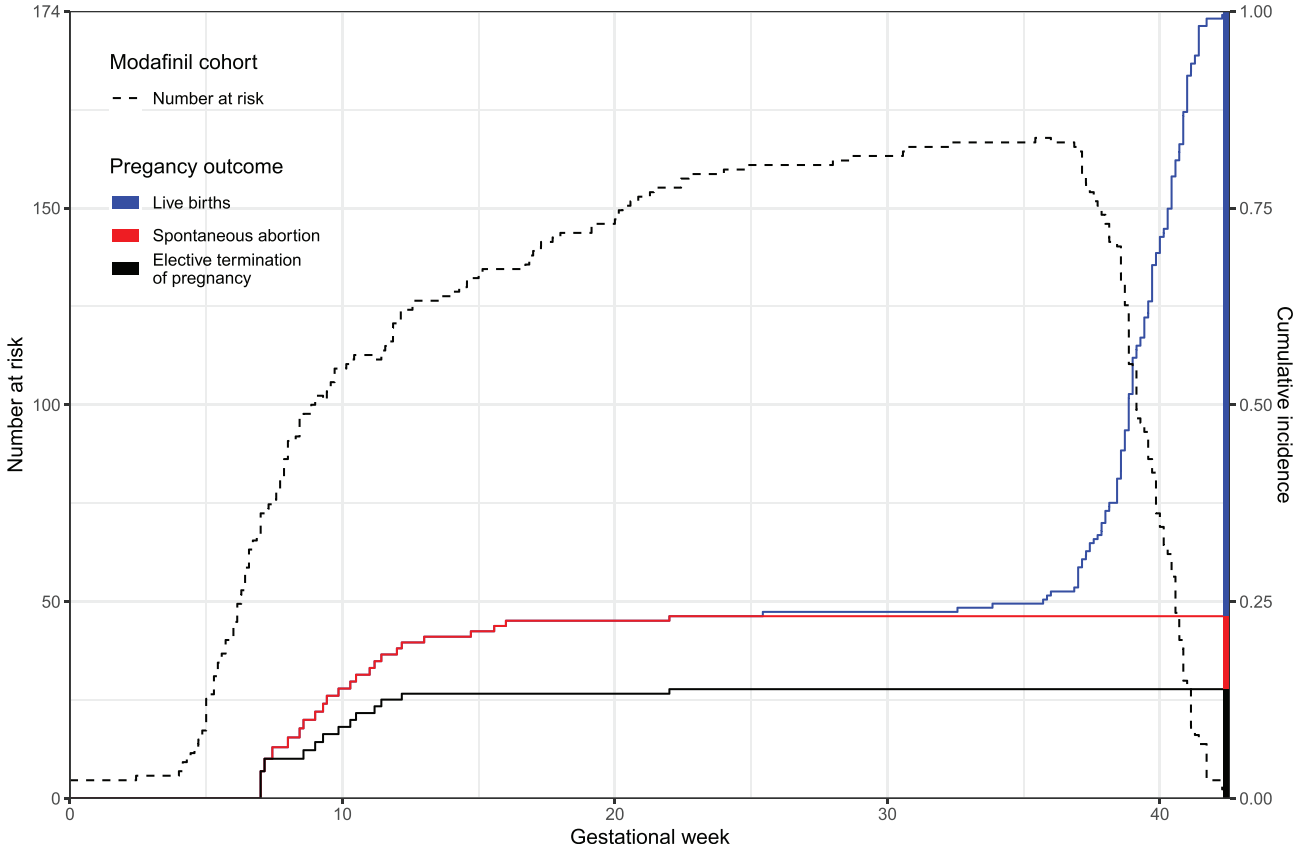

FIGURE 2 **Cumulative incidences of spontaneous abortion, elective termination of pregnancy, and live births.** The dotted line shows number of pregnancies at risk at a certain gestational age.

TABLE 2 Neonatal characteristics of live born children.

Gestational week, $N = 152$[a]	
Gestational week at birth[b]	39.57 (38.6–40.6) (25.4–42.6)
Preterm birth, *N* (%)	8 (5.3)
Term birth, *N* (%)	144 (94.7)
Neonatal sex, $N = 149$[a]	
Female, *N* (%)	75 (50.3)
Male, *N* (%)	74 (49.7)
Birth weight, $N = 148$[a]	
Birth weight[b] in g	3153 (2850–3483) (595–4200)
Neonatal length, $N = 93$[a]	
Neonatal length[b] in cm	49.5 (48–51) (35–55)
Neonatal head circumference, $N = 74$[a]	
Neonatal head circumference[b] in cm	34 (33.75–35) (30–37)

[a]Study cases with sufficient information for analysis, including one set of twins.
[b]Median, interquartile range, and min/max are presented.

21 without MCA. There were 3/150 live born infants with nonchromosomal MCA, corresponding to an MCA rate of 2.0% (95%CI, 0.6%–6.1%). No MCA was reported among pregnancy losses. One of the affected children presented with unilateral foot malformation and additional anomalies, another with Pierre Robin sequence, and a third neonate with esophageal atresia. For further details, see Table S5.

3.5 | Neonatal characteristics

Neonatal characteristics of prospectively ascertained study cases were overall unremarkable, they are presented in Table 2. In addition, no relevant differences were identified between newborns of narcolepsy patients and those of patients with other treatment indications (data not presented separately).

3.6 | Neonatal growth parameters

Sufficient data to calculate BW and HC percentiles were available for $N = 144/153$ (94.1%) and $N = 73/153$ (47.7%) newborns, respectively. For case details by contributing country, see Tables 3 and 4. In the modafinil

TABLE 3 Distribution of birth weight percentiles in live births (overall and separately for all countries contributing more than 10 observations to this analysis).

Live births overall	**Expected proportion in %** —	**All countries** $N = 153$	**France** $N = 71$	**Germany** $N = 20$	**Israel** $N = 14$	**Spain** $N = 10$	**Other countries**[a] $N = 38$
Live births with data on BW, sex and GW[b,c] at delivery	—	**$N = 144$ (94.1%)**	**$N = 64$ (90.1%)**	**$N = 20$ (100%)**	**$N = 14$ (100%)**	**$N = 10$ (100%)**	**$N = 36$ (94.7%)**
Percentile range[d]							
<3rd	3%	4.2% ($N = 6$)	7.8% ($N = 5$)	0% ($N = 0$)	0% ($N = 0$)	0% ($N = 0$)	2.8% ($N = 1$)
3rd–10th	7%	9% ($N = 13$)	7.8% ($N = 5$)	20% ($N = 4$)	14.3% ($N = 2$)	10% ($N = 1$)	2.8% ($N = 1$)
10th–25th	15%	20.8% ($N = 30$)	17.2% ($N = 11$)	25% ($N = 5$)	28.6% ($N = 4$)	40% ($N = 4$)	16.7% ($N = 6$)
25th–50th	25%	27.1% ($N = 39$)	23.4% ($N = 15$)	35% ($N = 7$)	21.4% ($N = 3$)	30% ($N = 3$)	30.6% ($N = 11$)
50th–75th	25%	20.8% ($N = 30$)	23.4% ($N = 15$)	15% ($N = 3$)	14.3% ($N = 2$)	20% ($N = 2$)	22.2% ($N = 8$)
75th–90th	15%	11.8% ($N = 17$)	14.1% ($N = 9$)	5% ($N = 1$)	21.4% ($N = 3$)	0% ($N = 0$)	11.1% ($N = 4$)
90th–97th	7%	4.2% ($N = 6$)	4.7% ($N = 3$)	0% ($N = 0$)	0% ($N = 0$)	0% ($N = 0$)	8.3% ($N = 3$)
≥97th	3%	2.1% ($N = 3$)	1.6% ($N = 1$)	0% ($N = 0$)	0% ($N = 0$)	0% ($N = 0$)	5.6% ($N = 2$)

[a]All countries contributing less than 10 cases to this analysis, that is, Australia ($N = 4$), Italy ($N = 2$), Japan ($N = 5$), Netherlands ($N = 1$), Switzerland ($N = 5$), Turkey ($N = 6$), the United Kingdom ($N = 9$), and the United States ($N = 4$). Group includes one set of twins. Since reference charts for twins were not available, percentiles for twins were calculated according to singleton reference charts. For both infants, percentiles of BW were above the median (percentile range 50th–75th).

[b]Gestational week.

[c]Birth weight.

[d]According to reference standards for each country as listed in Table S2. Percentiles were calculated according to neonatal sex and gestational week at delivery.

exposed cohort, BW tended to be lower and HC tended to be smaller compared to the reference populations: In 61.1% of in utero exposed newborns, BW was below the 50th percentile (see Table 3). In 54.8% of newborns neonatal HC was below the 50th percentile (61.3% and 68.4% in France and Germany, respectively), and below the 10th percentile in 15% (for further details see Table 4). However, none of the newborns were affected by severe microcephaly (HC < −3 SD), regardless of whether country-specific or international reference standards were used (Figure S1).

3.7 | Potential dose-dependent effects on fetal growth (BW and neonatal HC)

The linear regression models showed heterogeneous results among countries. In the overall cohort, each 100 mg increase of average modafinil dosage per pregnancy day was associated with a decrease in SD score of BW by −0.28 SDS (95% CI, −0.45 to −0.10). For details, see Figures S2 and S3, Table S6. Also for neonatal HC, each 100 mg increase of average dosage per pregnancy day was associated with a decrease in SDS of HC by −0.28 SDS (95% CI, −0.56 to 0.01), but the 95% CI contained zero. For details, see Figures S4 and S5, Table S7.

3.8 | Postnatal growth

A total of 41 of 153 live-born children (26.8%) were exposed long-term to modafinil (i.e., in all three trimesters). However, detailed information on postnatal growth parameters over the course of more than 1 month was available for only four of them ($N = 4/41$, 9.8%). In one infant, percentile ranges of weight and HC were continuously decreasing during the first year of life, but no overall trend of decreasing percentile ranges was seen in the other three infants. Figure S6 shows the respective growth curves.

3.9 | Retrospectively ascertained cases

Retrospectively ascertained cases were reviewed separately, and among the 22 retrospective cases, no specific pattern of congenital anomalies or other adverse events could be identified. All pregnancies were exposed at least during the first trimester of pregnancy. One neonate was affected by Pierre Robin sequence, another by duodenal atresia, and a third by a pelvic kidney. In one further case, a patent ductus arteriosus in a term neonate was reported. Two pregnancies were electively terminated after prenatal diagnosis of MCA, one because of spina bifida, the other because of

TABLE 4 Distribution of head circumference percentiles in live births (overall and separately for all countries contributing more than 10 observations to this analysis).

Live births overall	**Expected proportionin %** —	**All countries** $N = 153$	**France** $N = 71$	**Germany** $N = 20$	**Other countries**[a] $N = 62$
Live births with data on HC, sex and GW[b,c] at delivery	—	$N = 73$ (47.7%)	$N = 31$ (43.7%)	$N = 19$ (95%)	$N = 23$ (37.1%)
Percentile range[d]					
<3rd	3%	6.8% ($N = 5$)	9.7% ($N = 3$)	10.5% ($N = 2$)	0% ($N = 0$)
3rd–10th	7%	8.2% ($N = 6$)	6.5% ($N = 2$)	10.5% ($N = 2$)	8.7% ($N = 2$)
10th–25th	15%	15.1% ($N = 11$)	12.9% ($N = 4$)	26.3% ($N = 5$)	8.7% ($N = 2$)
25th–50th	25%	24.7% ($N = 18$)	32.3% ($N = 10$)	21.1% ($N = 4$)	17.4% ($N = 4$)
50th–75th	25%	21.9% ($N = 16$)	19.4% ($N = 6$)	21.1% ($N = 4$)	26.1% ($N = 6$)
75th–90th	15%	16.4% ($N = 12$)	12.9% ($N = 4$)	10.5% ($N = 2$)	26.1% ($N = 6$)
90th–97th	7%	2.7% ($N = 2$)	3.2% ($N = 1$)	0% ($N = 0$)	4.3% ($N = 1$)
≥97th	3%	4.1% ($N = 3$)	3.2% ($N = 1$)	0% ($N = 0$)	8.7% ($N = 2$)

[a]All countries contributing <10 cases to this analysis, that is, Australia ($N = 4$), Italy ($N = 1$), Japan ($N = 5$), Spain ($N = 4$), Switzerland ($N = 3$), Turkey ($N = 1$), the United Kingdom ($N = 2$), and the United States ($N = 3$). Group includes one set of twins. Since reference charts for twins were not available, percentiles for twins were calculated according to singleton reference charts. For both infants, percentiles of neonatal HC were above the median (percentile ranges 90th–97th and >97th).

[b]Gestational week.

[c]Head circumference.

[d]According to reference standards for each country as listed in Table S2. Percentiles were calculated according to neonatal sex and gestational week at delivery.

sirenomelia. One stillborn fetus had multiple anomalies, including facial dysmorphia, rhizomelia of arms, and hydrops fetalis.

4 | DISCUSSION

This multicenter case series of 175 exposed pregnancies is the largest investigation of prenatal modafinil exposure to date. Furthermore, it is the first evaluation of neonatal growth parameters after modafinil exposure in utero and the first investigation of potential dose-dependent effects.

The **MCA rate** of 2.0% in the Modafinil exposed cohort is within the prevalence ranges reported by EUROCAT registries[21,22] and does not constitute a signal for teratogenicity in terms of birth defects. Moreover, prenatal modafinil exposure in the newborn affected by esophageal atresia was very early (GW 0–2 + 3) and a causal modafinil effect does not appear plausible. Furthermore, no specific pattern of MCA was detected, though there were two infants with clinical diagnosis of Pierre Robin sequence, one among prospective and one among retrospective study cases. The prevalence of Pierre Robin sequence in the general population is estimated to be around 1: 8500–14,000.[23,24] Otherwise, none of the previously reported MCA[5,6,11] was found in the analyzed cohort. Our findings correspond to the nonincreased MCA rate of 2.3% among 133 exposed infants evaluated in the study by Cesta et al.[13]

Two other studies[11,12] present contrasting findings, even though it should be acknowledged that Damkier and Broe's[12] exposed group consisted of a relatively small sample size ($N = 49$). Furthermore, the high MCA rate of 13% reported by Kaplan et al.[11] raises relevant points of discussion, for two specific reasons: Four of the 13 birth defects assigned to MCA were congenital torticollis, not classified as MCA according to the EUROCAT classification guideline. In addition, there is no information on whether the manufacturer's database used for the study contained adequate details to accurately attribute the three cardiac and three nonspecified congenital anomalies to MCA.

The estimated cumulative incidence for **SAB** in our case series was 9.3% (95% CI, 5.0%–16.9%) which lies within the lower expected range for clinically recognized SAB in the general population.[25,26] As a competing event, however, the rate of ETOP was relatively high (13.9%, 95% CI, 8.1%–23.1%).

In the analyzed cohort, **BW** was lower than expected, in 34% of exposed newborns below the 25th percentile. Our exploratory linear regression model suggests a dose-dependent effect of modafinil exposure on BW. Apart from our analysis, there are no further evaluations of growth data after in utero exposure to modafinil. Interestingly, one small observational study found a higher BW in neonates of women with narcolepsy (majority not treated with modafinil) than in neonates of healthy women,[9] consistent with the metabolic changes and frequently increased BMI values typical for narcolepsy patients.[27] However, although more than 60% of women in our sample were also treated for narcolepsy, BW was inversely affected.

Regarding neonatal **HC**, our findings showed a tendency toward a negative correlation between average dosage per pregnancy day and HC, but the 95% CI contained zero and clinical relevance remains unclear. The evaluation of **postnatal growth** in infants with long-term exposure to modafinil in utero was limited to four informative cases and revealed no clear trend.

There are limitations to our study design, in particular the lack of a comparison group. Our sample sizes (overall and country-specific) are rather small, and most participating centers did not contribute data across the entire dosage spectrum. A relevant amount of data on specific maternal characteristics were missing, and we had to deal with substantial heterogeneity of data sets and information from different countries. The different reference charts on growth parameters in particular presented a challenge. We could not adjust the findings for potential confounding factors with a known impact on fetal growth. Thus, we cannot rule out the possibility that unmeasured confounding, for example confounding by indication or disease severity, is partly or even fully responsible for the observed effects. As for the biological plausibility of reduced fetal growth, the pharmacological effects of modafinil on the fetoplacental unit, for example via orexinergic pathways, are not sufficiently understood.[28] Overall, our findings of neonatal growth parameters should be interpreted with caution as a potential signal for an inhibiting effect of maternal modafinil intake on fetal growth, which has to be thoroughly investigated in further studies.

Given the conflicting results observed in different studies and populations, including the results presented here and those published by others, current evidence remains insufficient to draw definitive conclusions regarding risks associated with prenatal modafinil exposure. To provide definite clarification of the health authorities' warnings issued in 2019, further studies are needed. However, it might prove difficult to conduct observational studies with a sufficiently large number of exposed pregnancies, due to the fact that data sources suited for studies on drug safety during pregnancy do not necessarily contain information on off-label prescriptions or misuse of modafinil. Furthermore, not all data sources include growth data.

In conclusion, this ENTIS multicenter case series does not indicate an increased risk of MCA after in utero exposure to modafinil, but a tendency toward lower BW and reduced neonatal HC was noted. Our findings should be regarded as preliminary and will have to be confirmed or refuted by future studies. Until more data is available, modafinil should not be used during pregnancy.

AFFILIATIONS

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CONFLICT OF INTEREST STATEMENT

The study was not funded. ODC is currently the President of the European Network of Teratology Information Services (ENTIS). JLR is staff member of the UK Teratology Information Service, which is funded by the UK Health Security Agency, an

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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