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## Optimizing an algorithm for the identification and classification of pregnancy outcomes in German claims data

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1 **Optimizing an Algorithm for the Identification and Classification of Pregnancy Outcomes in**

2 **German Claims Data**

3 **Running head:** Pregnancy Outcomes in German Claims Data

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22 **Keywords:** Pharmacoepidemiology, Pregnancy outcomes, German claims data

23 **Key points**

24 • We optimized an existing algorithm to specifically identify and classify births in  
25 German claims data, which is the first essential methodological prerequisite for using  
26 these data for the subsequent study of drug utilization and safety during pregnancy.

27 • Overall, we identified 1,235,261 pregnancy outcomes, of those 94% live births  
28 (preterm (10%), term (78%) and (12%) births after the expected delivery date), 0.3%  
29 still births, 3.6% induced abortions, 1.3% ectopic pregnancies and 0.5% spontaneous  
30 abortions.

31 • Most results were plausible regarding the age distribution (median age 32 years) and  
32 sequence of outcomes (>99%) and in agreement (95%) with case profile review by  
33 clinical experts.

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41 **Abstract**

42 Purpose: For studying drug utilization and safety in pregnancy based on administrative  
43 health care data, the reliable identification and classification of pregnancy outcomes in the  
44 data is essential. We aimed to optimize an existing algorithm for the identification and  
45 classification of pregnancy outcomes in the German Pharmacoepidemiological Research  
46 Database (GePaRD) with a particular focus on births.

47 Methods: We reconsidered all codes used by the original algorithm and applied it to data of  
48 GePaRD from 2006 to 2014. Longitudinal records of pregnancies were used to identify  
49 targets for enhancing the algorithm's specificity. We checked the plausibility of the results,  
50 e.g. regarding the age distribution of persons with pregnancy outcomes. Based on 20  
51 longitudinal records of pregnancies, we compared the outcome classification by clinical  
52 experts with the results of the modified algorithm.

53 Results: Our algorithm identified 1,235,261 pregnancy outcomes in the database, with the  
54 majority (94%) being live births, classified as preterm (10%), term (78%) and (12%) births  
55 after the expected delivery date. The median age of pregnant women was 32 years (Q1 28;  
56 Q3 35). Implausible sequence of outcomes (for example an induced abortion within a  
57 pregnancy categorized as ending in a live birth) were rare (0.03%). The case profile review by  
58 clinical experts resulted in the same outcome type and date as the algorithm in 95%.

59 Conclusion: Our algorithm led to plausible results regarding the identification and  
60 classification of pregnancy outcomes. It will be an important foundation for studies on drug  
61 utilization and drug safety during pregnancy based on GePaRD.

## 62 **Introduction**

63 A considerable proportion of women use drugs during pregnancy, but at the time of market  
64 approval the safety of drugs during pregnancy is mostly unknown<sup>1-3</sup>. For an appropriate  
65 benefit-risk assessment of drug treatment during pregnancy, post-marketing safety  
66 evaluation is of major public health importance. Administrative health care (i.e. claims)  
67 databases are an important data source for studying drugs during pregnancy as they allow  
68 monitoring drug utilization and investigating the association between individual exposures  
69 and pregnancy outcomes in a timely manner and avoid recall bias<sup>4,5</sup>. Before a claims data  
70 base can be used for drug utilization and safety studies, the following three methodological  
71 procedures need to be established: (i) the reliable identification of pregnancy outcomes such  
72 as live births including preterm, term births, and births after the expected delivery date and  
73 classification of still births, induced or spontaneous abortions, and ectopic pregnancies<sup>6</sup> and  
74 their outcome date, (ii) the estimation of the beginning of pregnancy to assess gestational  
75 age at exposure during pregnancy and (iii) a linkage of the mothers' and the children's  
76 records to conduct drug safety studies focusing on the health of the child, e.g.  
77 malformations or developmental disorders.

78 In our study, we focused on the first of these methodological procedures. For the  
79 identification of pregnancy outcomes in claims or medical record data, particular caution is  
80 required because on person-level several codes like diagnoses and procedures may  
81 represent the same pregnancy outcome or diagnoses may be coded for administrative  
82 purposes. For example, a diagnosis could be recorded upon suspicion or to justify treatment  
83 (e.g. "preterm birth" as the reason for a hospital stay to avoid preterm birth). Furthermore,  
84 coding errors, implausible codes and implausible sequence of codes like an induced abortion

85 shortly before a live birth may occur. Algorithms are therefore needed to identify and  
86 classify pregnancy outcomes and assign their date, taking into account the reliability and  
87 plausibility of the respective codes and their combinations. Mikolajczyk et al. (2013)<sup>6</sup> have  
88 developed such an algorithm for the German Pharmacoepidemiological Research Database  
89 (GePaRD). We aimed to optimize this algorithm in terms of increasing its specificity, with a  
90 particular focus on live births for the subsequent analysis of drug-mediated outcomes in the  
91 child.

## 92 **Methods**

### 93 *Data source and study population*

94 We used data from 2006 to 2014 from GePaRD which contains information from four  
95 statutory health insurance providers (SHI) covering more than 20 million people from all  
96 regions in Germany. Data available in GePaRD include sex and year of birth, inpatient  
97 delivery dates, inpatient diagnoses (i.e. admission, discharge, and potentially secondary  
98 diagnoses) and outpatient diagnoses according to the German Modification of the  
99 International Classification of Diseases (ICD-10-GM), in- and outpatient procedures according  
100 to the Operations and Procedures Coding System (OPS), outpatient services, procedures  
101 according to the Doctors' Fee Scale within the Statutory Health Insurance Scheme  
102 (Einheitlicher Bewertungsmaßstab, EBM), and outpatient drug dispensations<sup>1,7</sup>. The sources  
103 differ in terms of the information provided, e.g. for outpatient procedures (OPS) only the  
104 quarter and the year are available.

105 Our study population included all persons with at least one pregnancy outcome between  
106 2006 and 2014. The rationale for not restricting our population to women of reproductive

107 age was to investigate how often pregnancy outcomes were coded in women outside of the  
108 childbearing age or in men.

109 *Algorithm to identify pregnancy outcomes and their corresponding date in GePaRD<sup>6</sup>*

110 For each pregnancy, a number of ICD, OPS, and EBM codes (and respective dates) are  
111 recorded over time in claims data, providing information that may be consistent or  
112 redundant but that could also be inconsistent (e.g. a live birth shortly after an induced  
113 abortion). To select the most plausible and valid information and to assign the correct date  
114 to the outcome, the previously developed algorithm<sup>6</sup> uses two nested hierarchical  
115 approaches. The first hierarchy determines an order for the different pregnancy outcome  
116 types, namely births, induced abortions, ectopic pregnancies, and spontaneous abortions  
117 (see Table 1, left column). This order is based on the assumption that indicators for births  
118 actually reflect births whereas ectopic pregnancies can also be coded in case of suspected  
119 (and later ruled out) diagnoses. Also, spontaneous abortions may be suspected diagnoses or  
120 could be coded as reasons for treatment to avoid the outcome. Therefore, the outcome  
121 “birth” with the respective date is considered most unambiguous and identified first.  
122 Furthermore, it is assumed that codes indicating induced abortions do not represent  
123 suspected diagnoses but that the induced abortion actually occurred. Hence, these  
124 outcomes are considered in the second place. As indicators for ectopic pregnancies may  
125 reflect suspected diagnoses but are more specific and less common than spontaneous  
126 abortions, they are identified in the third place. Finally, spontaneous abortions are assumed  
127 to be the most unspecific outcome and are therefore assessed last. In such way, if codes  
128 indicating ectopic pregnancies or spontaneous abortions were followed by live births within  
129 the same pregnancy, we could discard these earlier codes as not being true outcomes.

130 The second hierarchy is applied within each pregnancy outcome type. It takes into account  
131 that in the claims records there are typically various codes for a pregnancy outcome from  
132 different sources of information. This information may be redundant, but could also be  
133 conflicting regarding the date of the outcome. The algorithm therefore ranks the different  
134 sources of information according to their presumed level of validity when defining the date  
135 of the pregnancy outcome: inpatient delivery dates, inpatient OPS and ICD codes and  
136 outpatient EBM and OPS codes and their respective dates. Inpatient delivery dates, for  
137 example, are assumed to have the highest validity for births and specifically indicate the  
138 date of birth. Inpatient OPS codes are considered next because they also have a specific  
139 date. Inpatient diagnoses do not have an exact date, but generally, indicators from the  
140 inpatient setting are considered as more valid than from the outpatient sector. Outpatient  
141 OPS codes are considered last because they do not have a specific date.

142 Given that a woman can have multiple pregnancy outcomes during the study period - either  
143 of the same or a different type - it is essential to define which codes (and their dates) reflect  
144 the same pregnancy outcome and which sequences of codes are separate pregnancy  
145 outcomes. Hence, outcome-specific time frames, more specifically, a minimum “pregnancy  
146 duration” are defined as 259 days before a term birth (or birth after the expected delivery  
147 date), 154 days before a preterm or still birth, 49 days for an induced abortion and 42 days  
148 for ectopic pregnancies and spontaneous abortions. If more than one code for the same  
149 outcome occurs within these time frames, the most plausible outcome date is chosen  
150 specifically for each outcome type, e.g. for two delivery dates the date with an OPS code is  
151 assumed to reflect the true date of birth.

152 These time frames were also used to disregard codes according to the hierarchy of  
153 pregnancy outcomes, e.g. an ectopic pregnancy before a live birth.



154 *Modification of algorithm*

155 Our modification of the algorithm was performed in an iterative process: First, we assessed  
156 all codes used in the original algorithm<sup>6</sup> in cooperation with gynecologists and updated them  
157 (codes available from the authors). Based on longitudinal records of all pregnancy related  
158 outcome codes during manually selected pregnancies, we investigated the plausibility of the  
159 algorithm's outcome classification. This also allowed identifying targets to enhance the  
160 algorithm's specificity. We adapted the selection of codes and the structure of the algorithm  
161 accordingly. In detail, we limited the selection of ICD, OPS, and EBM codes to specific codes  
162 for each pregnancy outcome type. For example, our updated algorithm does not consider  
163 codes for providing care to a woman recently having given birth or wound infection after an  
164 obstetrical procedure as indicators for a birth because these codes often were used with a  
165 long delay after the pregnancy and thus might not be a good indicator of a birth. Regarding  
166 the identification of births, we restricted the inpatient diagnoses to main discharge and  
167 other main diagnoses. For induced and spontaneous abortions and ectopic pregnancies, we  
168 only included main discharge and other main diagnoses given that the review of longitudinal  
169 records during pregnancy showed inconsistencies when considering other types of inpatient  
170 diagnoses. In addition to the original algorithm, we also considered outpatient OPS codes for  
171 the identification of ectopic pregnancies. Regarding the classification of births, we  
172 introduced the category "birth after the expected delivery date" in order to be able to  
173 account for potentially longer pregnancy durations when estimating the beginning of  
174 pregnancy. To define births after the expected delivery date, we considered all inpatient  
175 diagnoses as it is very unlikely that these represent suspected diagnoses. To classify births as  
176 preterm and still births, we included all types of inpatient diagnoses except for admission

177 diagnoses as those could be suspected diagnoses that are either ruled out or later confirmed  
178 in a main discharge diagnosis.

179 After several adaptations, we re-implemented the modified algorithm.

#### 180 *Plausibility check of the modified algorithm*

181 We assessed the number of pregnancy outcomes and the frequency of the various types of  
182 pregnancy outcomes based on the modified algorithm. We evaluated the contribution of the  
183 various sources of information (i.e. delivery dates, inpatient OPS codes, etc.) in the  
184 determination of the outcome. To check the plausibility of the results of the modified  
185 algorithm, we analyzed the sex and age distribution of persons with a pregnancy outcome  
186 and the frequency of implausible sequences of outcomes within a pregnancy such as an  
187 induced abortion within a pregnancy ending in a live birth.

188 In addition, 20 randomly selected longitudinal records of codes during pregnancy covering all  
189 types of outcomes were reviewed by two clinical experts. For this review, we only selected  
190 pregnancies that have not been used to refine the algorithm. The aim of this review was to  
191 assess whether medical experts would use the same or other information for the  
192 identification and classification of pregnancy outcomes and process it in a similar way as our  
193 algorithm.

## 194 **Results**

### 195 *Pregnancy outcomes: Identification, date assignment, and classification*

196 Overall, the algorithm identified 1,235,261 pregnancy outcomes in the study period, of those  
197 1,164,743 were live births (94.3%), 3,190 still births (0.3%), 44,013 induced abortions (3.6%),  
198 16,659 ectopic pregnancies (1.3%) and 6,656 spontaneous abortions (0.5%).

199 Most of the live births (86.3%) were identified based on the source of information with the  
200 highest validity, i.e. an inpatient delivery date, and this information was used to assign the  
201 date of birth. For 12.5% of live births, an inpatient OPS code was used to determine the date  
202 of the outcome and for a minority (1.0%), inpatient ICD codes were used (Table 2). Live  
203 births in the outpatient setting (i.e. for which only outpatient codes were available) were  
204 rare (0.2%) and most of them were assigned an exact date based on an EBM code.

205 Overall, 10% of live births were classified as preterm, 78% as term, and 12% as birth after the  
206 expected delivery date.

207 The contribution of the various sources of information to determine the date of induced  
208 abortions, ectopic pregnancies and spontaneous abortions is shown in Table 2

#### 209 *Plausibility of the results*

210 The median age at the end of the year of the pregnancy outcome for women was 32 years  
211 (interquartile range IQR 28-35, see Figure 1 for further information).

212 We observed a considerable number of codes for a pregnancy outcome recorded for  
213 newborns like an OPS code “postnatal care for a newborn”. This explained the vast majority  
214 (>99%) of pregnancy outcomes identified in male persons (i.e. codes were assigned to male  
215 newborns). The remaining number of pregnancy outcomes identified in men was 604 out of  
216 more than 1,150,000 entries. In these men, we identified a variety of different codes for  
217 pregnancy outcomes that may be - either mistakenly or for administrative reasons -  
218 recorded in the health record of the father. Some combinations, e.g. a single code for  
219 induction of labor in an 85-year old are obvious coding errors. Further coding errors may  
220 occur regarding the sex in core data. Another explanation for pregnancy outcomes in men  
221 may be actual pregnancies before changing sex.

222 The results of the algorithm showed few implausible sequences of outcomes, such as a code  
223 for an induced abortion during a pregnancy (=within 259 days before and up to 42 days after  
224 an outcome classified as live birth) which were initially identified, but discarded by the  
225 algorithm in 393 pregnancies.

226 For all 20 longitudinally analyzed records reviewed by two clinical experts (blinded to the  
227 results of the algorithm), the outcomes identified and classified by the experts were the  
228 same as the outcomes from the algorithm (100%). For 19 profiles (95%), also the same  
229 outcome date was selected by the algorithm and the clinical experts and for one profile  
230 (spontaneous abortion) a discrepancy regarding the outcome date was observed. This  
231 discrepancy was caused by a code ('missed abortion') that we didn't select for our algorithm  
232 as it is not necessarily a final outcome.

## 233 **Discussion**

234 We optimized and implemented an algorithm that more specifically identifies and classifies  
235 pregnancy outcomes, particularly preterm, term and births after the expected delivery date  
236 based on German claims data, which is the first of three procedures for using these data to  
237 investigate drug utilization and drug safety during pregnancy.

238 In our study, 1,235,261 pregnancy outcomes were identified, with the majority being live  
239 births. More than 98% of live births were identified through an inpatient delivery date or an  
240 inpatient OPS code which means that the date of birth could be assigned based on these  
241 most unambiguous sources of information in almost all live births.

242 The study implementing the original algorithm on GePaRD<sup>6</sup> showed that the percentages of  
243 births and ectopic pregnancies agreed well with representative data for Germany, whereas

244 induced and spontaneous abortions were identified to a lesser extent<sup>6</sup>. The percentages in  
245 our study support this observation: The proportion of stillbirths in our study of 0.3% was well  
246 in line with national statistics<sup>8</sup>, whereas the proportion of spontaneous abortion of 0.5% was  
247 much smaller than expected based on literature, e.g. in a multicenter study in three different  
248 gynecological centers in Germany (average 3.3%)<sup>9</sup>. This can occur due to several reasons. For  
249 example, pregnancy outcomes for which no medical care is sought like unrecognized early  
250 losses - although relevant - can generally not be identified in studies based on administrative  
251 claims data. Further, we only used inpatient data for the identification of spontaneous  
252 abortions as outpatient diagnoses are only available on a quarterly basis and are generally  
253 less reliable than hospital diagnoses (e.g. they may present suspected diagnoses or history).  
254 We assume that by this we most likely only identified relatively late spontaneous abortions,  
255 which may also explain the low proportion. Induced abortions without a medical or  
256 criminological indication are usually not reimbursed by health insurance providers and can  
257 thus not be identified based on claims data either. We focused, however, on live births as an  
258 essential prerequisite for the investigation of potentially drug-mediated outcomes in the  
259 child such as developmental disorders. Other potentially drug-mediated outcomes such as  
260 spontaneous abortions, induced abortions, and perinatal death shortly after birth are also  
261 important outcomes to be studied based on GePaRD, but were not - although relevant - in  
262 the focus of our analysis.

263 Our data do not include claims of midwives, so non-identification of live births would be  
264 relevant for deliveries solely accompanied by midwives. However, in 2014 only 1.3% of all  
265 deliveries in Germany were out-of-hospital deliveries<sup>10</sup> and births taking place solely in  
266 midwife-led-units in hospitals are assumed to be few due to only 15 units of this kind in  
267 Germany<sup>11</sup>. To identify those children in the data it is possible to use proxies such as claims

268 for routine examinations for small children, but this was not in the focus of our study.  
269 Overall, we think that an underestimation of the total number of live births played only a  
270 minor role.

271 We classified birth outcomes into still births and preterm or births after expected delivery  
272 date according to inpatient diagnoses. The proportion of preterm births was well  
273 comparable with national statistics (10% as compared to 8.9%<sup>8</sup>). The coding of preterm,  
274 term and births after the expected delivery date in the database is based on the  
275 reimbursement rules. In claims data, birth after the expected delivery date is any birth after  
276 the expected day of delivery, as the reimbursable care (e.g. midwife visits) increases after  
277 the expected day of delivery. As expected, the proportion of deliveries after the expected  
278 date is considerably higher than the proportion of postterm births in national statistics (12%  
279 as compared to 0.6%<sup>8</sup>). The relevance of this sub-classification will be evaluated in future  
280 studies that aim to determine the beginning of pregnancy in GePaRD (e.g. based on the date  
281 of specific examinations).

282 In our study, an implausible sequence of codes occurred only very rarely. For example, in  
283 393 out of 1.16 million pregnancies (0.03%) classified as ending in a live birth by the  
284 algorithm, we observed a code indicating an induced abortion 154-259 days before or  
285 shortly after the birth outcome. The codes for induced abortion in these cases may reflect  
286 coding errors which justifies discarding them from the analysis. For 65 births, the algorithm  
287 identified a code indicating an induced abortion on the same day as the birth outcome,  
288 which may reflect late termination of pregnancy. Late abortions were not in the focus of this  
289 modified outcome algorithm, but will be assessed in more detail in the context of drug  
290 safety studies.

291 The age distribution of persons with a pregnancy outcome in our study was plausible and - in  
292 terms of live births - well in agreement with national statistics. The mean age of women  
293 giving birth in Germany overall was 31 years in 2015<sup>12</sup> as compared to 31.5 years during our  
294 study period. For the vast majority of persons with a pregnancy outcome at an implausible  
295 age, we could identify the reason. This was predominantly caused by codes referring to  
296 newborns (e.g. postnatal care for a newborn) that may be recorded either for the mother or  
297 her child. When these codes were recorded for the child, the algorithm identified newborns  
298 aged 0 years as having a birth outcome. In some cases, the corresponding mother may be  
299 identified by linkage of mother-baby pairs<sup>1</sup>. This is an important prerequisite to investigate  
300 the association between the mothers' drug utilization during pregnancy and the fetal  
301 outcome. This linkage is the third procedure for studying drug safety in pregnancy and an  
302 existing algorithm<sup>1</sup> will be updated based on experiences with our study.

303 When using German claims data for studies on drug utilization and drug safety during  
304 pregnancy, the second of three essential procedures is to determine the beginning of  
305 pregnancy (and thus the gestational age) as there are critical time windows of exposure for  
306 many drugs. Since the beginning of pregnancy is not directly available in administrative  
307 claims data, several algorithms were developed to estimate the beginning of pregnancy<sup>5</sup>.  
308 German administrative claims data have not been explored in this regard yet, but our  
309 algorithm identifying pregnancy outcomes and assigning the respective date is an important  
310 prerequisite to estimate, in a next step, the beginning of pregnancy based on GePaRD.

## 311 **Conclusion**

312 We optimized an algorithm to identify and classify pregnancy outcomes, particularly births,  
313 in GePaRD and to assign the respective dates. The algorithm showed plausible results and a

314 high level of agreement based on clinical expert review of pregnancy profiles. This algorithm  
315 is the first procedure for using GePaRD for studies on drug utilization and drug safety during  
316 pregnancy.

317



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326

327 **Conflict of interest**

328 NW, TS, MN, SU and UH are working at the Leibniz Institute for Prevention Research and  
329 Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by  
330 the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies  
331 (PASS) requested by health authorities. The studies and the resulting publications are not  
332 influenced by the pharmaceutical industry.

333 RM declares no conflict of interest.

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372

373

374 **Tables and Figures**

375 **Table 1: Hierarchical structure of the algorithm i) regarding the pregnancy outcomes and ii) the**  
 376 **sources of information**

<b>Hierarchy of the outcomes</b>	<b>Hierarchy of the sources of information</b>	<b>Availability of an exact outcome date</b>
<b>I. Births</b>	<b>I.a.</b> Inpatient delivery date	Yes
	<b>I.b.</b> Inpatient procedure (OPS)	Yes
	<b>I.c.</b> Inpatient diagnosis (ICD)	Yes†
	<b>I.d.</b> Outpatient service (EBM)	Yes
	<b>I.e.</b> Outpatient procedure (OPS)	No
<b>II. Induced abortions</b>	<b>II.a.</b> Inpatient procedure (OPS)	Yes
	<b>II.b.</b> Outpatient service (EBM)	Yes
	<b>II.c.</b> Inpatient diagnosis (ICD)	Yes†
	<b>II.d.</b> Outpatient procedure (OPS)	No
<b>III. Ectopic pregnancies</b>	<b>III.a.</b> Inpatient procedure (OPS)	Yes
	<b>III.b.</b> Inpatient diagnosis (ICD)	Yes†
	<b>III.c.</b> Outpatient procedure (OPS)	No
<b>IV. Spontaneous abortions</b>	<b>IV.a.</b> Inpatient diagnosis (ICD)	Yes†

377

378 † Here, the date of hospital admission was used as it is likely to be closer to the date of the  
 379 outcome than the date of discharge from hospital.

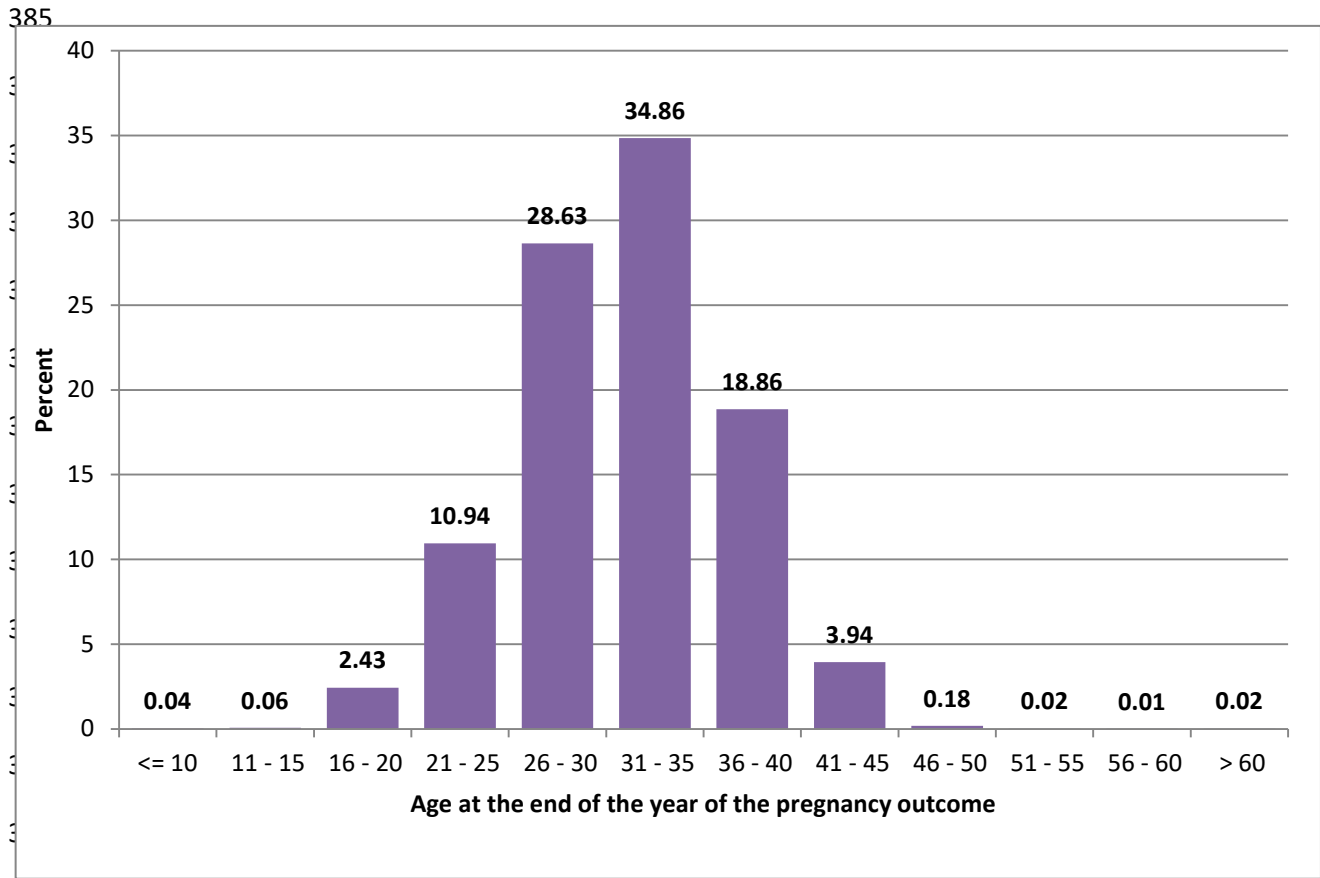
380

381 **Table 2: Contribution of sources for pregnancy outcomes**

Outcome/ Source of information	Live births N Column %	Still births N Column %	Induced abortions N Column %	Ectopic pregnancies N Column %	Spontaneous abortions N Column %	∑ Row %
Inpatient delivery date	1,004,965 86.28	2,917 91.44	NA	NA	NA	1,007,882 81.59
Inpatient procedure (OPS)	146,029 12.54	244 7.65	7,542 17.14	10,780 64.71	NA	164,595 13.32
Inpatient diagnosis (ICD)	11,203 0.96	26 0.82	2,099 4.77	5,642 33.87	6,656 100	25,626 2.07
Outpatient service (EBM)	2,221 0.19	3 0.09	34,207 77.72	NA	NA	36,431 2.95
Outpatient procedure (OPS)	325 0.03	0 0.0	165 0.37	237 1.42	NA	727 0.06
∑ Column %	1,164,743 94.29	3,190 0.26	44,013 3.56	16,659 1.35	6,656 0.54	1,235,261 100

382

383 **Figure 1: Distribution of age among female persons with at least one pregnancy outcome during**  
384 **the study period**



398

399 This includes female persons with information on the year of birth. Newborns were excluded.