بسمه تعالی
دانشگاه علوم پزشکی تبریز

تاریخ:.....
شماره:.....
پیوست:.....

فرم گزارش دوره ای پایانی [√] طرح تحقیقاتی

اعتبار شده از محل ۱ درصد ماده ٥٦ قانون الحاق ۲

(توسط مجری طرح تکمیل گردد.)

عنوان طرح : راه اندازی و توسعه نظام ثبت ناهنجاریهای مادرزادی		شماره قرارداد: ۷۰۰/۲۰۳
نام مجری: دکتر سعید دستگیری	مدت زمان اجرای کل طرح: ۳ سال	تاریخ عقد قرارداد: ۱۳۹٤/۱۰/۲۰
شماره مصوب شورای پژوهشی دانشگاه ۱۰۱۰۱۱۱/د/ه		

خلاصه اقدامات انجام شده:

با عرض سلام و احترام،

بدینوسیله مستندات و گزارش خلاصه شده ای از فعالیت های انجام شده در ارتباط با برنامه های "ناهنجاری مادرزادی" را لطفا به پیوست

ملاحظه فرمائید که شامل موارد ذیل می باشد:

- گزارش فعالیت های انجام شده در ارتباط با برنامه های "ناهنجارهای مادرزادی"
- ضمیمه اول گزارش: گزارش رجیستری ناهنجارهای مادرزادی در ایران
- ضمیمه دوم گزارش: فایل اعتبار یابی بررسی سوابق سلامت خانوادگی بیماری های مادرزادی
- ضمیمه سوم گزارش: فصل اپیدمیولوژی بیماری های مادرزادی در ایران در کتاب اپیدمیولوژی و کنترل بیماریهای شایع در ایران
- ضمیمه چهارم تا یازدهم گزارش: انتشارات مقالات انگلیسی مربوط به برنامه ناهنجاری های مادرزادی (در طول طرح حاضر)

(ضمنا سه مقاله دیگر نیز از این داده ها پذیرش شده و در حال چاپ می باشد.)

لیست اموال خریداری شده، غیر مصرفی و سرمایه ای:
یک دستگاه لپ تاپ
یک دستگاه تبلت

بسمه تعالی
دانشگاه علوم پزشکی تبریز

تاریخ:.....
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میزان پیشرفت کار طرح به عدد: ۱۰۰ درصد به حروف: صد در صد

امضاء مجری طرح:

تاریخ: ۱۳۹۷/۱۱/۱۳

امضاء ناظر قرارداد در دانشگاه

تاریخ:

تائید شورای پژوهشی دانشگاه

تاریخ:

امضا معاون پژوهشی دانشگاه:

تاریخ:

مراتب فوق مورد تائید می باشد: امضاء رییس دانشگاه
مراتب فوق بررسی شد و مورد تائید می باشد. ناظر معاونت: ناظر معاونت: امضاء مشاور اجرائی معاونت تحقیقات و فناوری امضاء قائم مقام معاونت تحقیقات و فناوری تاریخ: تاریخ:
تذکر: فرم فوق بدون تائید و توشیح مسئولین فوق الذکر (مجری طرح، شورای پژوهش، معاونت پژوهشي، ریاست دانشگاه و مهر دانشگاه) فاقد اعتبار می باشد.

باسمه تعالی

گزارش فعالیت های انجام شده در ارتباط با برنامه های "ناهنجاری مادرزادی"

دکتر سعید دستگیری

برنامه رجیستری بیماری های مادرزادی ابتدا به صورت یک برنامه پایلوت در شمال غرب کشور شروع و پس از چند سال از اجرای منطقه ای و تدوین الگوهای لازم برای برنامه کشوری، اکنون این رجیستری به صورت ملی اجرا می شود. طرح حاضر تحت عنوان "توسعه نظام ثبت ناهنجاریهای مادرزادی" که از سال ۱۳۹٤ اجرا می گردد تاکنون دستاوردها و فعالیت های ذیل را داشته است:

- **کتاب "پایش ناهنجاری های مادرزادی در ایران" (برای اولین بار در ایران)**
- **کتاب "اطلس ناهنجاری های مادرزادی در ایران" (برای اولین بار در ایران)**
- **ایجاد، مدیریت و نگهداری وب سایت برنامه ملی ثبت، اپیدمیولوژی و پایش ناهنجاری های مادرزادی (escai.ir)**
- **اعتبار یابی برنامه منطقه ای پایش ناهنجاری های مادرزادی (مقاله مربوطه منتشر شده است)**
- **ادامه اعتبار یابی برنامه کشوری پایش ناهنجاری های مادرزادی (حدود ده سال دیگر نیز ادامه خواهد داشت)**
- **برنامه "تجمع فامیلی" بیماری های مادرزادی در منطقه اسد آبادی (ادامه دارد)**
- **تهیه گاید لاین کنترل و پیشگیری ناهنجاری های مادرزادی در ایران**
- **کارگاه ها و دوره های آموزشی و اجرائی متعدد در سازمان ها و شهرهای مختلف کشور**
- **ادامه عضویت ملی این برنامه در دو نهاد بین المللی ICBDSR, EUROCAT (با پرداخت حق عضویت ارزی)**
- **ارائه گزارش سالانه اول، دوم و سوم برای برنامه کشوری (مجموعا در ۱٤۲۱ صفحه)**
- **انتشار یازده مقاله در طول اجرای طرح فعلی (هشت مورد چاپ شده و سه مورد در حال چاپ)**
- **تهیه و انتشار سه فصل در کتاب های تکست به زبان فارسی در کشور با عنوان ناهنجاری های مادرزادی در ایران (یک فصل در طول اجرای طرح حاضر، یک فصل دیگر در حال چاپ)**

(الف) رجیستری ناهنجاری های مادرزادی

همچنانکه قبلا گفته شد، تاکنون در ایران داده های نظام مندی از وقوع ناهنجاريهاي نوزادي وجود نداشته است. بر این اساس، مطالعات اولیه در ایران در سال ۱۳۷۹ در شمال غرب کشور با مشارکت چند نفر از همکاران (از جمله جناب آقای دکتر حیدرزاده) شروع شد. هدف کلی از این برنامه راه اندازی یک مرکز ثبت، کنترل و پیشگیری از ناهنجاری های مادرزادی و ژنتیکی با دور نمای تحقیقاتی و ارائه خدمات بهداشتی – درمانی به جمعیت در معرض خطر با تکیه بر برخی ویژگی های اپیدمیولوژی این بیماریها در ایران با اهداف ذیل بوده است:

- تعریف ساختار اپیدمیولوژیک ناهنجاری های مادرزادی در منطقه
- تعیین حداقل مجموعه داده ها برای ثبت و کنترل و پیشگیری ناهنجاریهای مادرزادی
- تعیین رویه های ثبت ناهنجاریهای مادرزادی
- تعیین منابع اولیه ثبت ناهنجاریهای مادرزادی
- ارایه الگوی مناسب ثبت ناهنجاریهای مادرزادی در کشور

این برنامه با این رویکرد دنبال شده است که بتواند پاسخگوی نیازهای اطلاعاتی کاربران مختلف باشد و نهایتا به کنترل و پیشگیری ناهنجاریهای مادرزادی و ارتقای سلامت کودکان کمک نماید.

بخشی از فعالیت های برنامه پایلوت ذیلا به صورت فهرست وار ارائه میشود:

- میزان شیوع کلی ناهنجاریهای مادرزادی برابر با ۳,۳ درصد تولد است.
- ناهنجاری های مربوط به دستگاه تناسلی، ادراری و کلیه، سیستم عصبی و دستها و پاها مجموعاً حدود هفتاد درصد از کل موارد را به خود اختصاص داده اند.
- از هر سه مورد از جنین های تشخیص داده شده برای ناهنجاری های مادرزادی، فقط یک مورد اجازه سقط پیدا می کنند.
- شصت درصد از نوزادان دارای ناهنجاریهای مادرزادی قلبی تشخیص داده نمی شوند.

- تدوین الگو ی بومی و دستورالعمل های پیشگیری از ناهنجاریهای مادرزادی در منطقه بر این اساس دستورالعمل های ارائه شده توسط سازمان جهانی بهداشت
- انتشار چندین ده مقاله چاپ شده (ایندکس سطح یک) و ارائه های متعدد در کنگره ها و سمینار ها و چاپ فصل های مرتبط در سه کتاب

لطفا بخشی از نتایج برنامه کشوری را نیز ذیلا ملاحظه فرمایید (نتایج تفصیلی برنامه کشوری برای سالهای را در **ضمیمه شماره یک** قابل مشاهده است):

- شیوع کلی ناهنجاری های مادرزادی در کشور ۲,۲ در صد تولد می باشد.
- ناهنجاری های چشم و گوش بیشترین و نقایص کروموزومی کمترین میزان را در کشور نشان می دهند.
- بیش از دو درصد از موارد تولد با ناهنجاری مادرزادی قبل از ترخیص از بیمارستان منجر به فوت شده اند.
- بیشترین شیوع ناهنجاری های لوله عصبی در استان سیستان و بلوچستان
- بیشترین شیوع ناهنجاری های دست و پا در استان یزد
- بیشترین شیوع ناهنجاری های شکاف کام و لب در استان یزد
- بیشترین شیوع ناهنجاری های کروموزومی در استان خراسان جنوبی
- بیشترین شیوع ناهنجاری های گردن و صورت در استان خراسان جنوبی
- بیشترین شیوع ناهنجاری های تناسلی و تناسلی در استان ایلام
- بیشترین شیوع ناهنجاری های گوارش در استان ایلام
- بیشترین شیوع ناهنجاری های سندروم داون در استان ایلام
- بیشترین شیوع ناهنجاری های گوش و چشم در استان خراسان رضوی
- بیشترین شیوع ناهنجاری های عضلانی و اسکلتی در استان سمنان
- بیشترین شیوع ناهنجاری های قلبی در استان سمنان
- بیشترین شیوع ناهنجاری های سیستم عصبی در استان لرستان

- بیشترین شیوع ناهنجاری های تعریف نشده در استان قزوین

طبق دستورالعمل سازمان بهداشت جهانی، تصمیم بر این است که برنامه کشوری (در صورت فراهم بودن شرایط و بودجه) در یک بازه زمانی ۱۵-۱۰ ساله اعتبار یابی شود که طبعا جزو اصول اساسی هر برنامه ثبت می باشد.

در حال حاضر نیز اعتبار یابی و چگونگی ادغام تشخیص و کنترل بیماری های مادرزادی در برنامه پزشکی خانواده به صورت پایلوت در حال بررسی و اجرا می باشد که نتایج امیدوارکننده ای تاکنون داشته است بطوریکه با توجه به هزینه بری بسیار بالای تعداد زیادی از این قبیل بیماری ها، نتایج اولیه نشان میدهد که میتوان از برنامه پزشکی خانواده برای تشخیص و کنترل بیماری های مادرزادی با هزینه بسیار ناچیز بهره برد.

(ب) وب سایت ناهنجاری های مادرزادی

معمولا رجیستری های استاندارد در سطح جهان بخشی از نتایج خود را برای استفاده عمومی منتشر می کنند. در سالهای اخیر برای نیل به این مقصود، از وب سایت های اختصاصی نیز استفاده میشود. از این وب سایت ها ی اختصاصی، ضمنا به عنوان وسیله ای برای گسترش حساس سازی و آگاهی های عمومی در آن موضوع خاص استفاده می شود. از سال گذشته برای برنامه کشوری ناهنجاری های مادرزادی یک وب سایت اختصاصی (به آدرس http://www.escai.ir) طراحی و در نظر گرفته شده است. در این وب سایت علاوه از انتشار بسیار خلاصه شده ای از نتایج سالانه وقوع بیماری های مادرزادی در کشور، تعدادی فایل ها و مطالب آموزشی نیز برای استفاده عموم قرار داده شده است. در چند ماه گذشته، سامانه دیگری با عنوان "بررسی سوابق سلامت خانوادگی" به این وب سایت اضافه شده که در واقع برای ارزیابی ریسک هر فرد برای ابتلا به بیماری هایی که احتمالا زمینه خانوادگی دارند مورد استفاده خواهد بود. تکمیل این پرسشنامه توسط هر فرد، ریسک مورد نظر برای هر فرد را ارزیابی و متناسب با آن راهنمائی های لازم را برای همان فرد انجام میدهد. برای این منظور یک پرسشنامه ای که قبلا در کشور های دیگر به این منظور استفاده می شود در ایران (در قالب یک پایان نامه پی اچ دی) بومی سازی شده و جزئیات نتایج بدست آمده در سامانه مورد اشاره

طراحی گردیده است (فرم اصلی به زبان انگلیسی را در **ضمیمه شماره دو** ملاحظه فرمائید. ضمنا با کلیک روی آیکون "بررسی سوابق سلامت خانوادگی" در وب سایت می توان وارد نسخه بومی سازی این سامانه شد و آن را تکمیل کرد).

(پ) انتشارات مربوط به برنامه ناهنجاری های مادرزادی (در طول طرح حاضر)

مقالات منتشر شده از این برنامه در دو سال اخیر نیز با فهرست ذیل در ضمیمه های سوم تا یازدهم قابل مشاهده است:

- اپیدمیولوژی بیماری های مادرزادی در ایران در کتاب اپیدمیولوژی و کنترل بیماریهای شایع در ایران تالیف: فریدون عزیزی، محسن جانقربانی، حسین حاتمی، تهران: دانشگاه علوم پزشکی و خدمات بهداشتی درمان شهید بهشتی و پژوهشکده علوم غدد درون ریز و متابولیسم، ۱۳۹۶. ویراست چهارم.
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ضمنا سه مقاله دیگر نیز از این داده ها پذیرش شده و در حال چاپ می باشد.

وزارت بهداشت، درمان، و آموزش پزشکی
برنامه ثبت و گزارش ناهنجاری های مادرزادی
<www.escai.ir>

گزارش

"رجیستری ناهنجاری مادرزادی در ایران"

دکتر سعید دستگیری

۱۳۹۷

تشکر و قدردانی

وزارت بهداشت، اداره نوزادان: جناب آقای دکتر محمد حیدرزاده و همکاران برای مدیریت برنامه

دانشگاه های علوم پزشکی کشور برای فراهم کردن داده ها

کارشناسان پروژه: آقای علی رفیعی، خانم سمیه الوندی، آقای بهرام ملکی

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- روش کار
- نتیجه گیری و بحث
- یافته های کلیدی

گزارش طرح

زمينه و اهميت

ناهنجاريهاي مادرزادي (Congenital Anomalies) به آن دسته از نقص ها ی تولد اطلاق مي شود كه نوزاد حين تولد (زنده يا مرده) آنها را دارا مي باشد . اين نقص ها شامل نقص هاي ساختماني ، اختلالات كروموزومي ، نقص هاي متابوليسم در هنگام تولد و بيماريهاي وراثتي مي باشد. بیماریهای وراثتی بخشی از ناهنجاریهای مادرزادی میباشند ولی تمام بیماریها مادرزادی الزاما ماهیت ژنتیکی و وراثتی ندارند. ناهنجاريهاي مادرزادي مي توانند از نظر اهميت باليني ، جزيی (Minor) يا عمده (Major) باشند و همينطور مي توانند به صورت موردي و يا به صورت چند ناهنجاري همراه در نوزاد بروز كنند.

بتدريج با كنترل بيماريهاي عفوني و سوء تغذيه، ناهنجاريهاي مادرزادي بعنوان اولين عامل مرگ و مير و ناتواني در دورة خردسالي محسوب مي شوند. اين موضوع بخصوص از نظر انتقال اپيدميولوژيك در جوامع در حال توسعه كه در آنها الگوهاي ابتلا بتدريج از بيماريهاي عفوني و سوء تغذيه به بيماريهاي غير عفوني تغيير مي يابد اهميت دارد. ناهنجاري هاي مادرزادی و اختلالات ژنتيكي مسئول بخش قابل توجهی از مرگ و مير، بيماريزايي و ناتواني در سراسر دنيا مي باشند اما بعلت تفاوت هاي نژادي و فرهنگي، شيوع اين اختلالات در مناطق مختلف بسيار متغير مي باشد.

در حال حاضر نقايص مادرزادي هنگام تولد مهم ترين علت مرگ و مير نوزادان بخصوص در جوامع توسعه يافته، علت سوم مرگ و مير و ناتواني در كودكان در كشورهاي در حال توسعه و همينطور علت اصلي مرگ و مير و ناتواني در جوامع توسعه يافته مي باشد. از اينرو كشورهاي در حال توسعه از هم اكنون مي بايست تخصيص منابع و امكانات خود را با توجه به الگوهاي ابتلا كه در حال انتقال از بيماريهاي غيرعفوني مي باشد ، چنان طراحي نمايند كه درآينده نزديك بخش قابل توجهي از آن را به پيشگيري و كنترل ناهنجاريهاي مادرزادي و ژنتيكي اختصاص دهند.

ناهنجاريها ي جزئي در ۱۵ درصد نوزادان وجود دارد در حالی که ناهنجاريهاي عمده مادرزادي در ۳ – ۲ درصد نوزادان زنده بدنيا آمده مشاهده ميشود و حدود ۳ درصد ديگر تا سن پنج سالگي به اين مقدار افزوده مي شود و در مجموع به حدود هشت درصد تا سن ۱۸ سالگي مي رسد. اين اختلالات در حالت كلي مسئول يك پنجم مرگ و ميرها مي باشند. از هر سه كودك بستري در هر كدام از بخش هاي بيمارستاني يك مورد از آنها بعلت ناهنجاريها و اختلالات ژنتيكي مي باشد. مجموعة اين بيماريها پنجمين علت اصلي كاهش طول عمر پيش از ۳۵ سالگي و از علت هاي اصلي ايجاد كننده معلوليت در كليه سنين مي باشند.

نقايص مادرزادي و عوارض بعدي آن در سنين بالاتر گروههاي نژادي مختلف را يكسان مبتلا مي كنند و همينطور ميزان مرگ و مير حاصل از انها نيز در ميان مردم جوامع آسيايي ، آفريقايي و آمريكاي لاتين تقريباً برابر است اما اين ميزانها در كشورهاي توسعه يافتة آمريكايي و اروپايي بعلت پيشرفتهاي تكنولوژي پزشكي و بالا بودن ميزان دسترسي به خدمات بهداشتي و سطح آگاهي هاي عمومي از علل و روشهاي پيشگيري از ناهنجاريهاي مادرزادي و ژنتيكي پائين تر از ساير جوامع مي باشد.

با وجود آنكه در حال حاضر اطلاعات فراواني از تاثير عوامل مختلف محيطي در وقوع ناهنجاريهاي مادرزادي از مطالعات آزمايشگاهي روي حيوانات آزمايشگاهي وجود دارد، اما هنوز اطلاعات جامعي در اين زمينه در جمعيت های انسانی وجود ندارد و بطور کلی حدود ۶۰-۴۰ درصد از علل وقوع ناهنجاريهای مادرزادی ناشناخته می باشند. با وجود اين از نظر عوامل موثر ، ناهنجاريهاي مادرزادي را به سه دسته تقسيم مي كنند:

الف) عوامل ژنتيكي

حداقل يك سوم از ناهنجاريهاي مادرزادي با علت شناخته شده منشاژنتيكي دارند. در اين زمينه اختلالات كروموزومي بخش قابل توجهي از ناهنجاريهاي مادرزادي را تشكيل مي دهند.

ب) عوامل محيطي

محل رشد جنين در رحم مادرمی تواند جنين را به خوبي از خطراتي كه در دورة بارداري وجود دارد، محافظت كند. با وجود اين عوامل محيطي مختلف مانند مصرف داروها، ويروس ها و ساير عوامل محيطي در دورة بارداري مي توانند جنين را با مخاطرات جدي كه منجر به ناهنجاريهاي مادرزادي خواهد شد مواجه سازند. برخي از اين عوامل مستقيماً جنين را در رحم مادر تحت تاثير قرار مي دهند و برخي نيز از طريق ايجاد اختلالات كروموزومي منجر به ناهنجاريهاي مادرزادي مي گردند. تعداد و تنوع عوامل محيطي مؤثر در ايجاد ناهنجاريهاي مادرزادي با تحقيقات جديد مرتباً افزايش پيدا مي كند. مواجهه مادر در دورة بارداري با دود سيگار، الكل، گازهاي بيهوشي، جيوه، ويروس سرخجه، سيتومگالوويروس ها، اشعه ها (مثل اشعه ايكس) و برخي داروها از عوامل ايجاد كننده ناهنجاريهاي مادرزادي هستند. هر چند اين عوامل مرتباً در حال گسترش هستند اما در مجموع اين عوامل حدود كمتر از ۱۰ درصد علل ناهنجاريهاي مادرزادي را تشكيل مي دهند .

بالا بودن سن مادر در هنگام تولد نوزاد، رتبه تولد بعد از دوم، فاصله گذاری كمتر از سه سال بين تولدها، برخي اختلالات تغذيه اي (مانند كمبود اسيد فوليك، آهن و بالا بودن مصرف ويتامين A)، ابتلاي مادر به ديابت و چاقي مادر نيز در سالهاي اخير از عوامل محيطي مؤثر در وقوع ناهنجاريهاي مادرزادي شناخته شده اند. همچنين نشان داده شده است كه زايمان هاي دو قلو بخصوص چند قلوزايي خطر وقوع ناهنجاريهاي مادرزادي افزايش مي دهد.

پ) عوامل توام ژنتيكي و محيطي

بسياري از ناهنجاريهاي مادرزادي بعلت نقش توام عوامل ژنتيكي و محيطي اتفاق مي افتند. اين موضوع بدين معني است كه اغلب ناهنجاريهاي مادرزادي ماهيت چند فاكتوري دارند. با وجود اين در حال حاضرامكان تفكيك نقش هر كدام از عوامل (محيطي و ژنتيكي) در وقوع ناهنجاريهاي مادرزادي و تعيين مقدار اثر مستقل هر كدام از آنها وجود ندارد اما بطور كلي عوامل توام ژنتيكي و محيطي حدود ۲۰ درصد ازعوامل ايجاد كننده ناهنجاريهاي مادرزادي را تشكيل مي دهند .

در کشور ما در هر سال حدود يك و نيم ميليون تولدزنده وجود دارد اما تخمين درستي از اينكه چه تعداد از اينها با ناهنجاريهاي مادرزادي متولد مي شوند در دست نيست. این امر ایجاب می کرد که یک برنامه ثبت در کشور ارائه شود. بر این اساس در ایران از سال ۱۳۸۲ یک برنامه پایلوت در این زمینه در دانشگاه علوم پزشکی تبریز با لحاظ كردن الگوهاي ثبت ناهنجاري هاي مادرزادي در حدود پنجاه كشور دنيا كه آن را اجرا می کنند با این اهداف شروع شده است: تعریف ساختار اپیدمیولوژیک ناهنجاری های مادرزادی در منطقه، تعیین حداقل مجموعه داده ها برای ثبت و کنترل و پیشگیری ناهنجاریهای مادرزادی، تعیین رویه های ثبت ناهنجاریهای مادرزادی، تعیین منابع اولیه ثبت ناهنجاریهای مادرزادی، و نهایتا ارایه الگوی مناسب ثبت ناهنجاریهای مادرزادی در کشور.

در نهایت از تجربیات برنامه فوق در شمال غرب کشور برای اجرای کشوری برنامه کشوری استفاده گردیده است. بطور مشخص در گزارش حاضر نیز بررسی و تحلیل وضعیت موجود کشور در مورد ناهنجاری های مادرزادی در چهار سال اجرای آن در استان ها ارائه میگردد تا با لحاظ نمودن اشکالات و خطاهای مربوطه، اجرای آن را برای سالهای بعدی ارتقا داد. تحلیل داده های این رجیستری در نهایت می تواند:

مواد لازم برای مدیریت های کلان برنامه های بهداشتی و درمانی نوزادان و مادران آسیب پذیر فراهم نماید

زمینه لازم برای پژوهش های مرتبط با ناهنجاری های مادرزادی و ژنتیکی را فراهم کند

الگوهای وقوع و اپیدمی های احتمالی از ناهنجاری های مادرزادی را به موقع تشخیص دهد

روش کار

داد ه های این گزارش، از کودکان متولد شده در مناطق تحت پوشش دانشگاههای علوم پزشکی کشور می باشند که با توجه به پرونده ها و تکمیل بودن آنها از لحاظ شرح حال باليني، برگه هاي آزمايشات تكميلي و تشخيص قطعي نوع ناهنجاري در هنگام تولد بر اساس نظريه متخصصين و عامل های زایمان حاضر در هنگام تولد نوزاد ويا مطالعات پاراكلينيكي بدست آمده است.

در اجرای کشوری برنامه ثبت، از تجربه پایلوت قبلی انجام شده در دانشگاه علوم پزشکی تبریز در طی دوازده سال گذشته نیز استفاده شد ه است. بر این اساس، نقص ها و یا ناهنجاري هاي مادرزادي (با تعریف ذکر شده در بخش قبلی) به آن دسته از اختلالات اطلاق مي شود که نوزاد در حین تولد (زنده یا مرده) آنها را دارا مي باشد. کلیه ناهنجاریها بر مبنای تعریف و کد بندی سیستم طبقه بندی بین المللی بیماری ها و کد گذاری اختصاصی انجمن پزشکی کودکان بریتانیا در یکي از گروههاي عمده زیر گروه بندي شده اند:

شکاف کام و لب، عضلانی و اسکلتی، دست و پا، ادراری و تناسلی، سیستم عصبی (بدون ناهنجاری های لوله عصبی)، کروموزومی (بدون سندروم داون)، سندروم داون، قلبی، لوله عصبی، گردن و صورت، گوارشی، گوش و چشم، تعریف نشده

نتیجه گیری و بحث

این گزارش به عنوان اولین مطالعه شیوع و وضعیت موجود از ثبت ناهنجاریهای مادرزادی در کشور ارائه شده است تا پس از رفع نقایص و اعتبار یابی آن بتوان یک برنامه ثبت معتبر و دائمی برای همه استانها در کشور برای سالهای آتی ایجاد نمود بطوریکه نتایج حاصل از آن نه تنها نیازهای کاربران سیستم های سلامت و پژوهش در کشور را در این زمینه فراهم می سازد، بلکه بتواند با نمونه های موجود در کشورهای توسعه یافته قابل مقایسه باشد.

در فراهم سازی این گزارش، موارد نسبتا متعددی از اشتباهات اطلاعاتی مرتبط با اپراتوری و مدیریت داده ها مشاهده گردید که آن موارد متاسفانه غالبا به علت عدم امکان پیگیری و دسترسی مجدد به منابع اولیه، ناچارا در آنالیز داده ها کنار گذاشته شد.

با وجود اینکه ورود و ثبت اطلاعات نوزاد بر مبنای کد ملی مادر تعریف شده است، در این زمینه حتی داد ه های متفاوتی با کد ملی مشابه و یا داد ه ها ی مشابهی با کد ملی متفاوت وجود داشت که تا حد امکان و با توجه به سایر اطلاعات موجود تصحیح گردید و در صورت عدم امکان اصلاح از مجموعه داد ه ها حذف گردید.

علاوه از خطاهای اپراتوری فوق، همچنانکه در بخش یافته ها ارائه گردید، وقوع کلی ناهنجاری های مادرزادی در برخی از استانها بسیار بیشتر و یا کمتر از حد مورد انتظار گزارش شده است و یا در مواردی نیز یک ناهنجاری خاصی به طرز نا معمول بیشتر و یا کمتر دیده می شود.

بر این اساس، بطور کلی برای اعتبار یابی و بهبود و ارتقا کیفیت داده ها برای سالهای آتی، موارد ذیل پیشنهاد می گردد:

الف) ارزیابی و بازبینی محلی در مواردی که شیوع کلی (و یا مورد خاصی از) ناهنجاری های مادرزادی کمتر یا بیشتر از حد انتظار اتفاق افتاده است

ب) ارزیابی و بازبینی محلی به صورت راندوم از تعدادی از بیمارستانها و دانشگاه های علوم پزشکی مشارکت کننده در برنامه

لازم به توضیح است که این ارزیابی ها به صورت موازی به دو شکل "ارزیابی داخلی" و "ارزیابی خارجی" صورت می گیرد که جزئیات بیشتر در یک برنامه اجرائی مجزا ارائه می گردد.

پ)اجرای دوره های آموزشی تکمیلی اختصاصی برای متخصصین و عامل های زایمان در دانشگاه های علوم پزشکی سراسر کشور

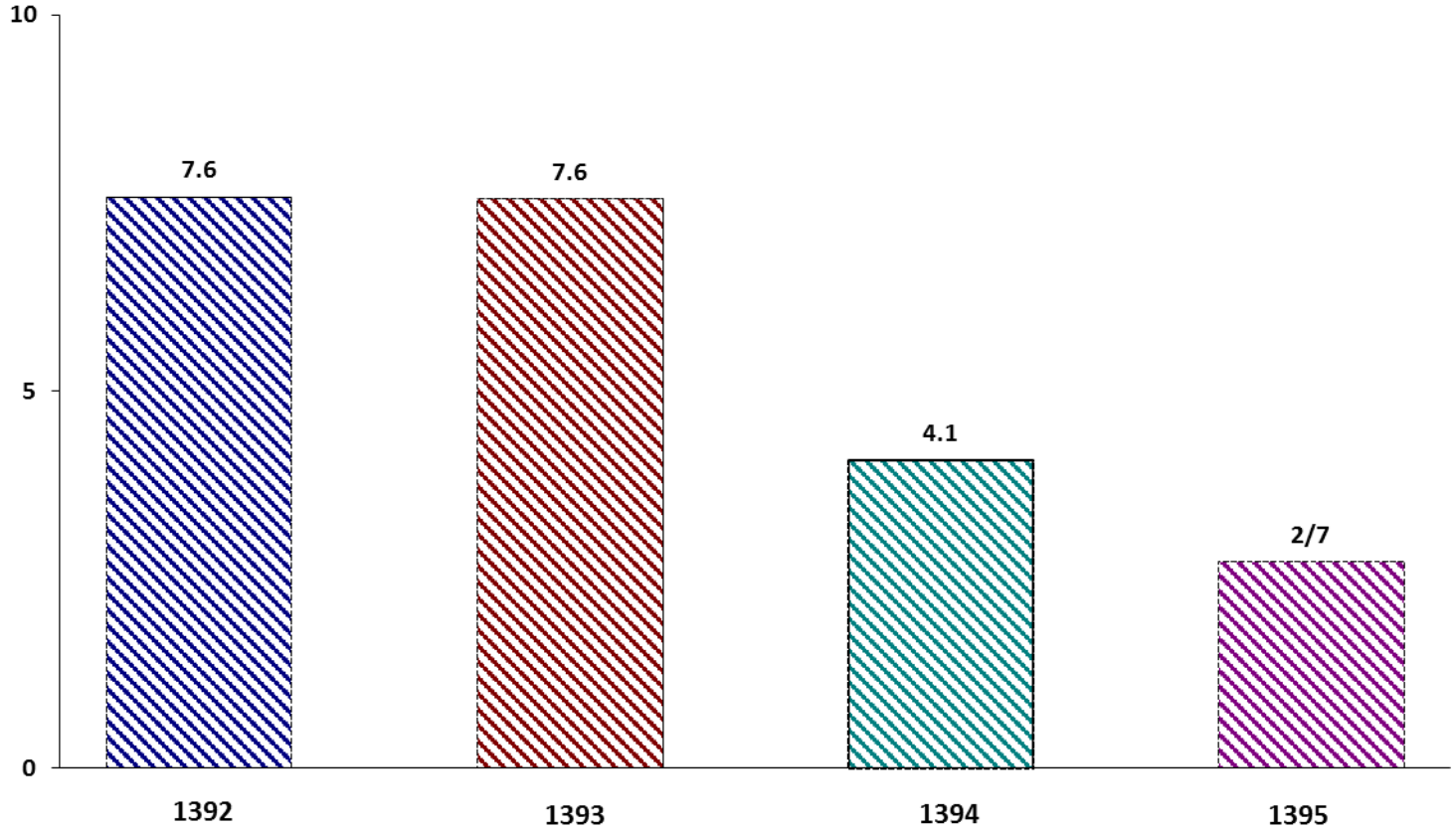
ت)اجرای دوره های آموزشی تکمیلی اختصاصی برای عوامل ثبت و اپراتوری و مدیریت داده ها در دانشگاه های علوم پزشکی سراسر کشور

ج)بتدریج با بهبود برنامه، داد ه ها ی بیشتری را نیز می توان به برنامه ثبت ناهنجاری های مادرزادی اضافه نمود که از آن جمله و با توجه به مطالعات قبلی موارد زیر پیشنهاد می گردد: سابقه خانوادگي، داده هاي آزمايشگاهي وسيتوژنتيكي، اطلاعات مربوط به اتيولوژي و اطلاعاتی درباره پیگیری و بقاي بيماران.

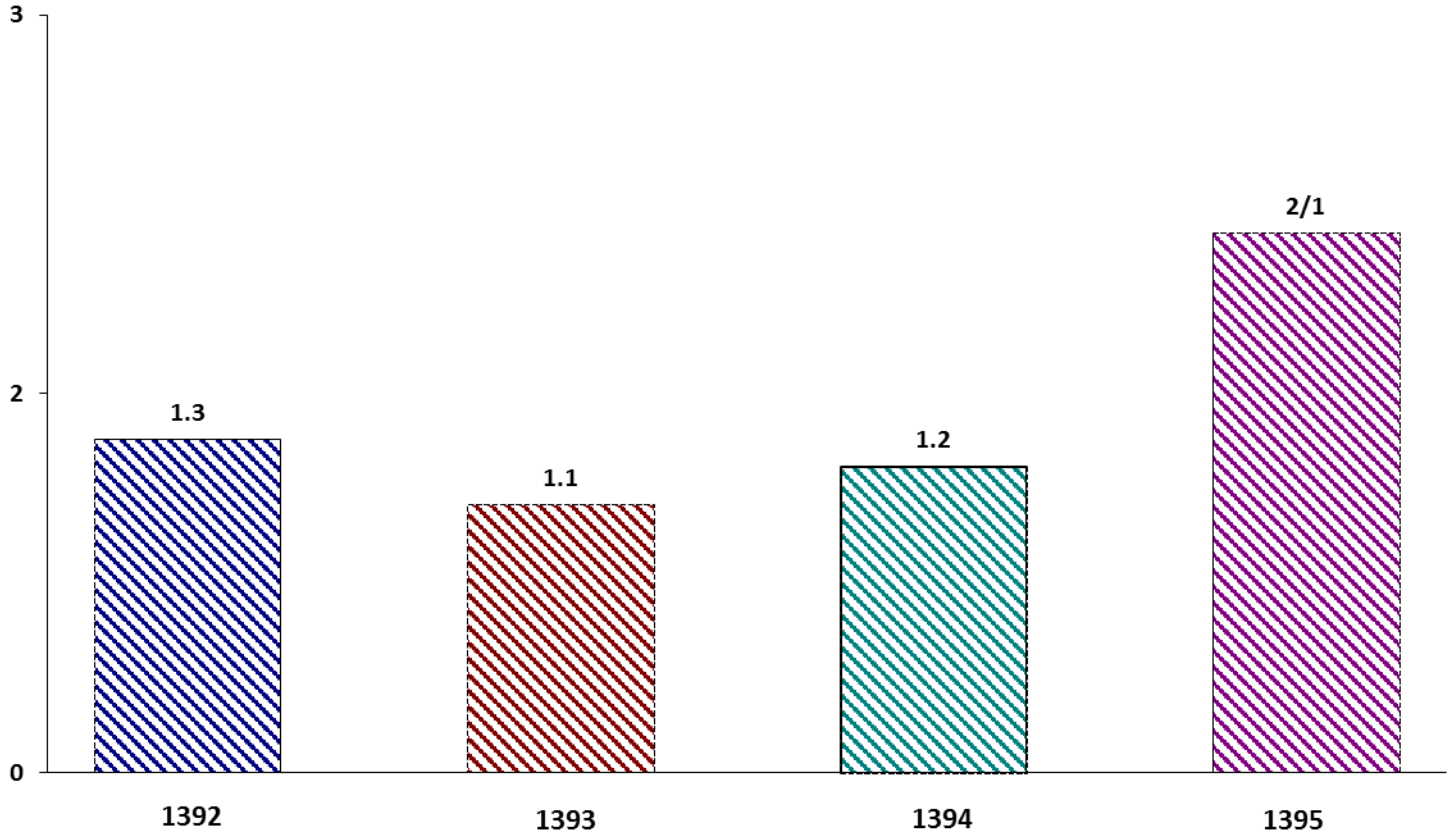
چ)در پایان و با ملاحظه موارد فوق، پیشنهاد می گردد که ترتیبی اتخاذ گردد تا این گزارش به صورت سالانه و روز آمد از روند وضعیت ناهنجاری های مادرزادی در کشور تهیه و ارائه گردد تا ضمن بکار گیری نتایج در کنترل این دسته از بیماری ها و همینطور کارکرد های پژوهشی مربوطه، وقوع هرگونه اپیدمی خاصی نیز شناسائی و اقدامات متناسب صورت گیرد.

یافته های کلیدی سالهای ۱۳۹۲ لغایت ۱۳۹۵

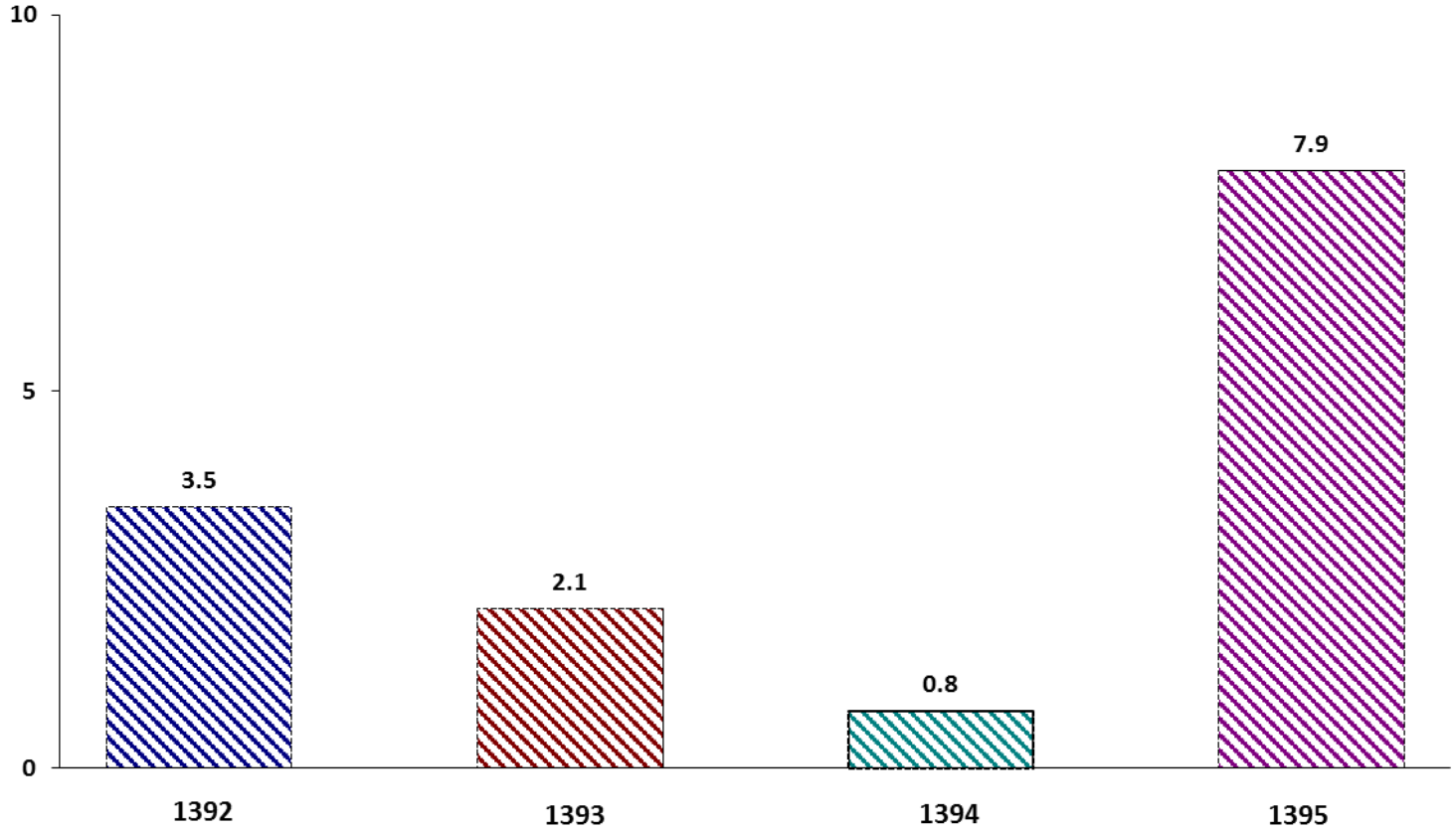
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در آذربایجان غربي (95 -1392)



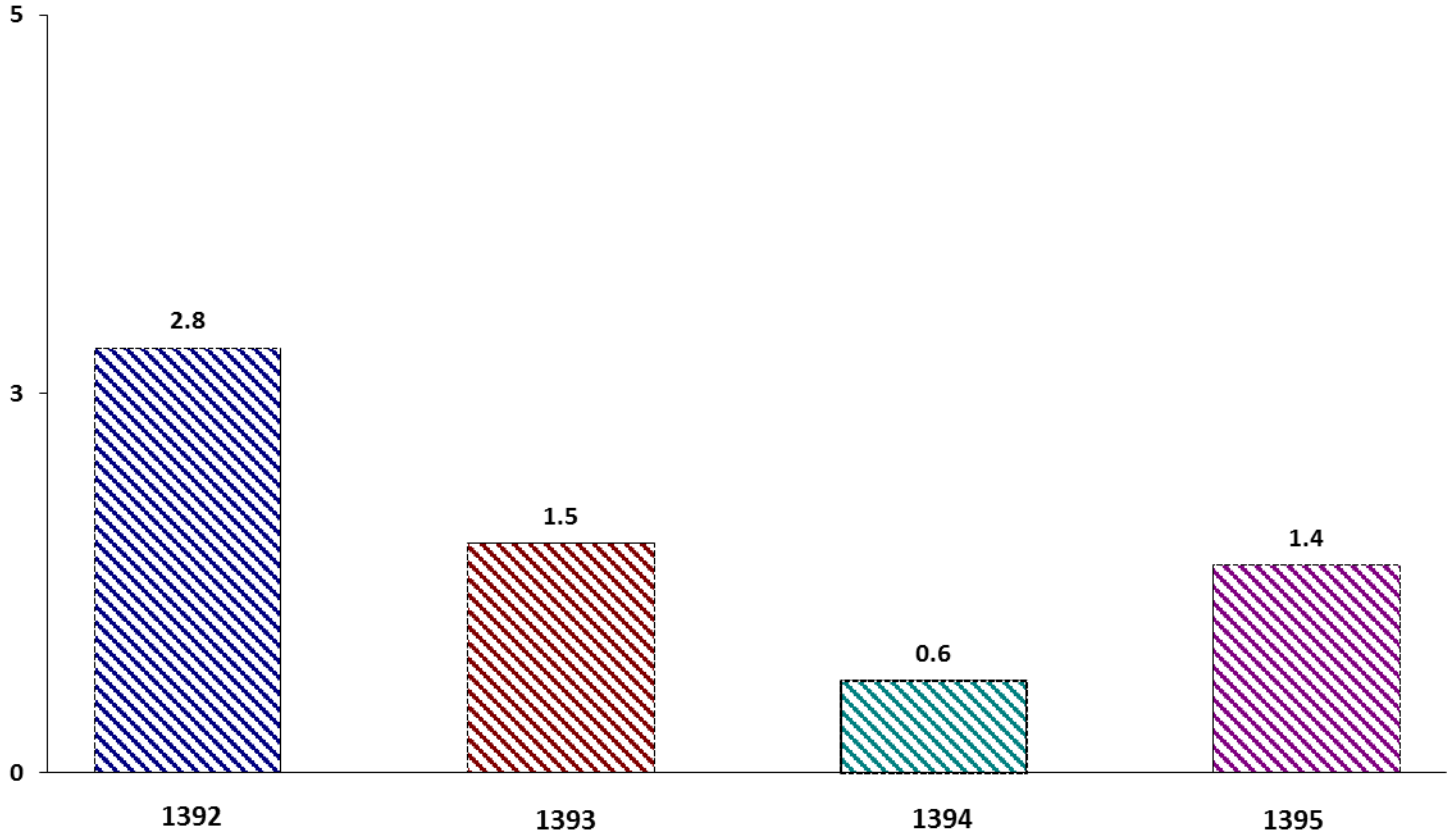
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در آذربایجان غربي در سال(95 -1392)



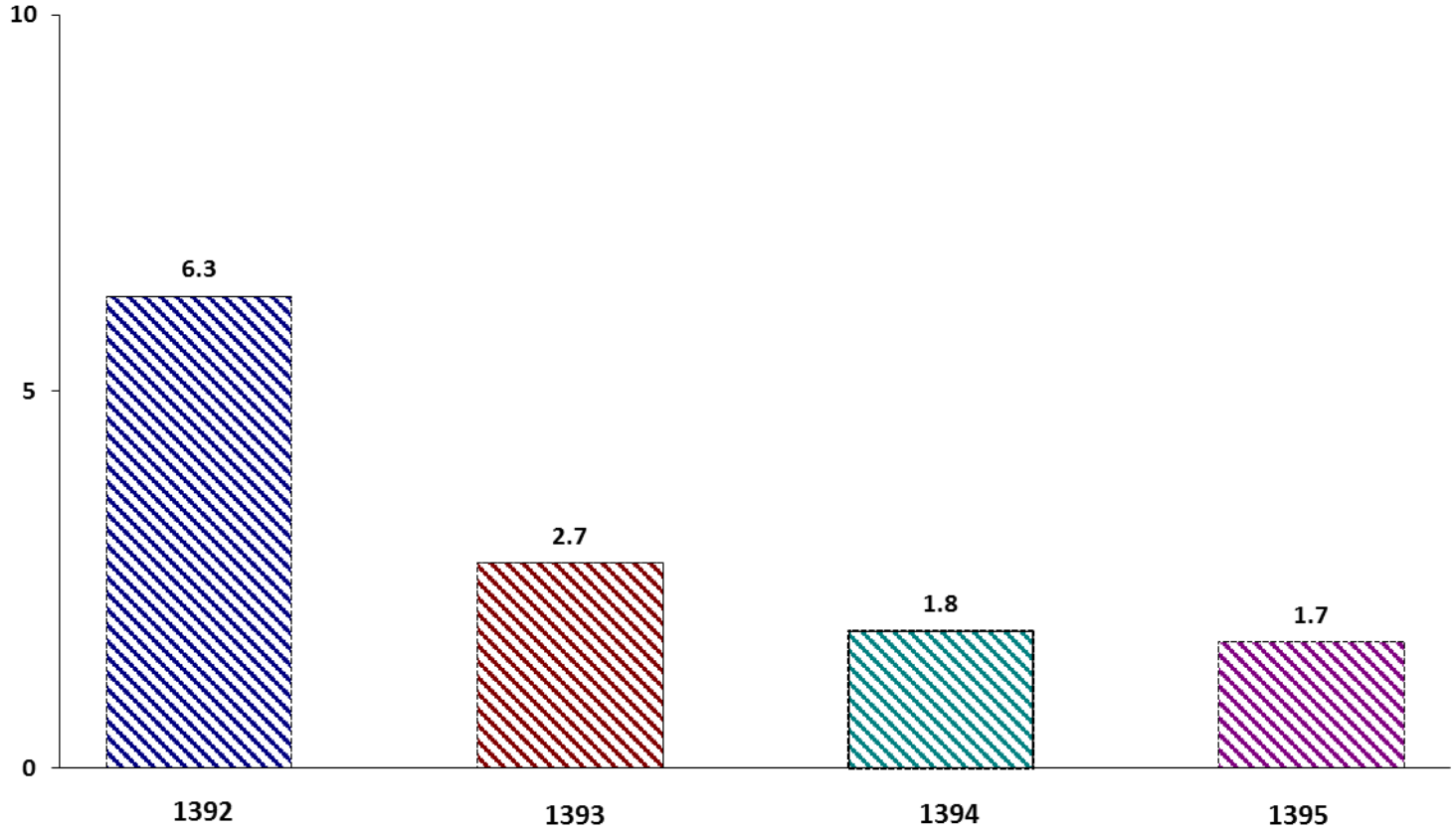
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در آذربایجان غربي (95 -1392)



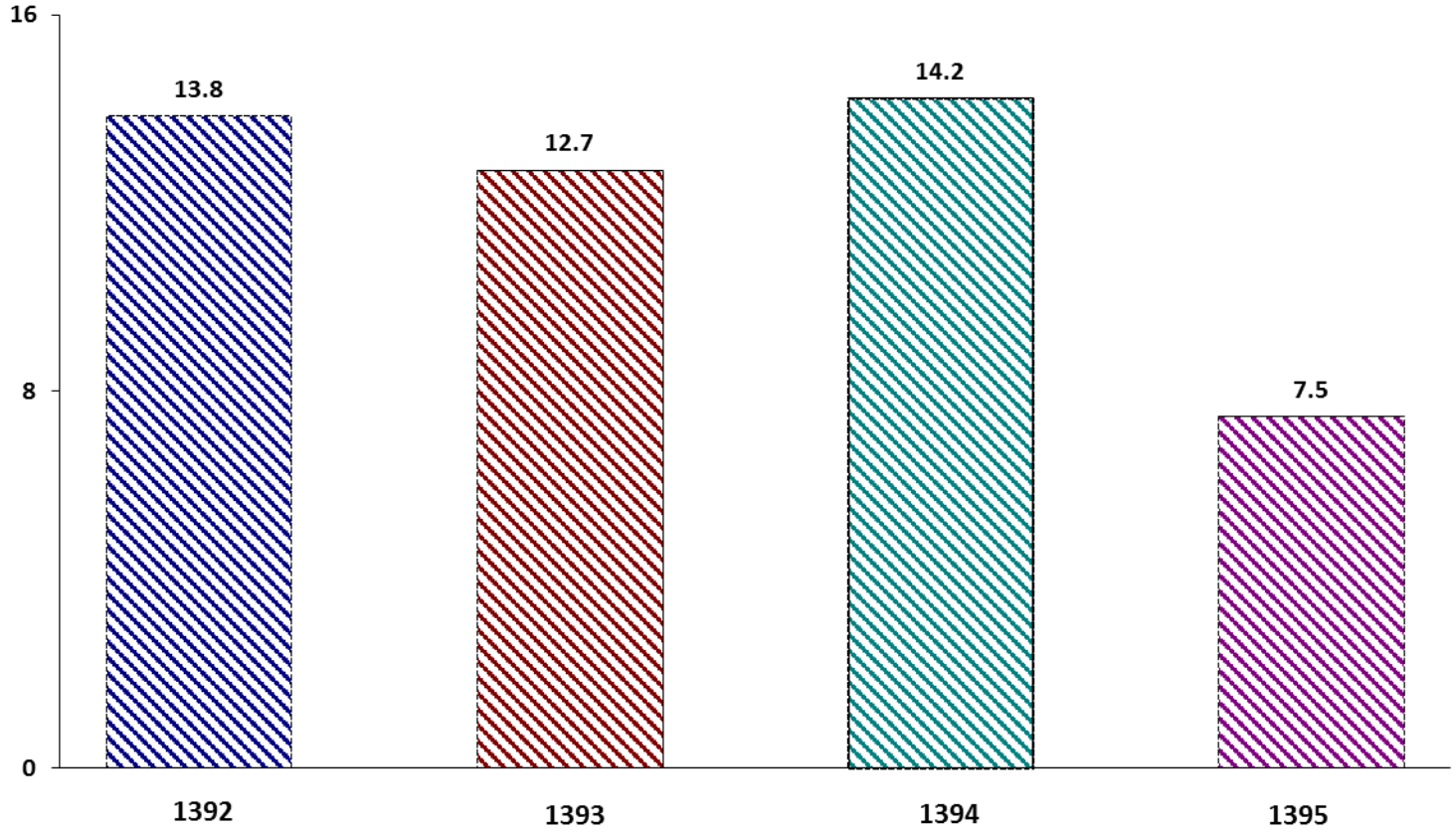
شیوع کلی ناهنجاری های مادرزادی قلبي (در هر ده هزار تولد) در آذربایجان غربي (95-1392)



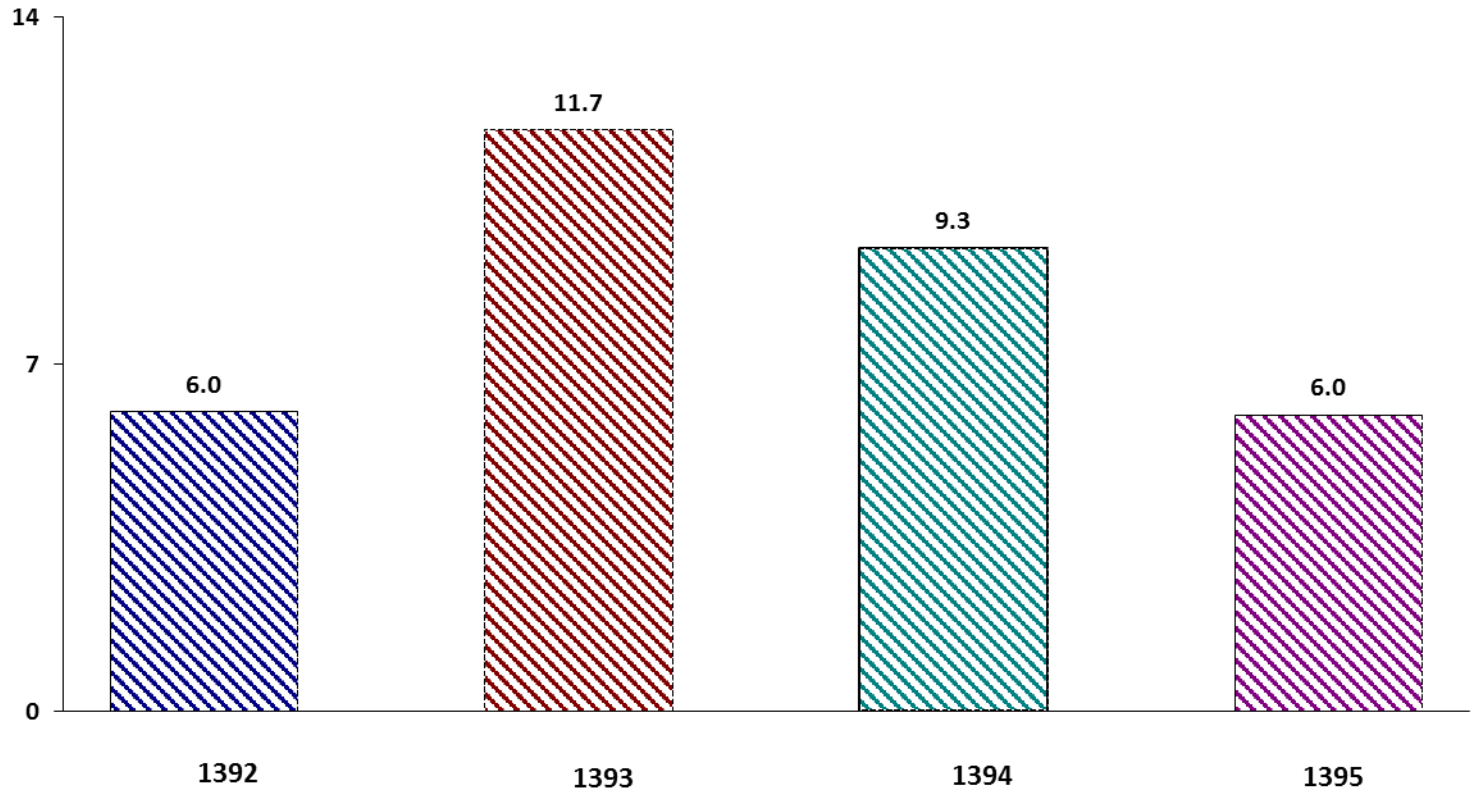
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در آذربایجان غربي (95 -1392)



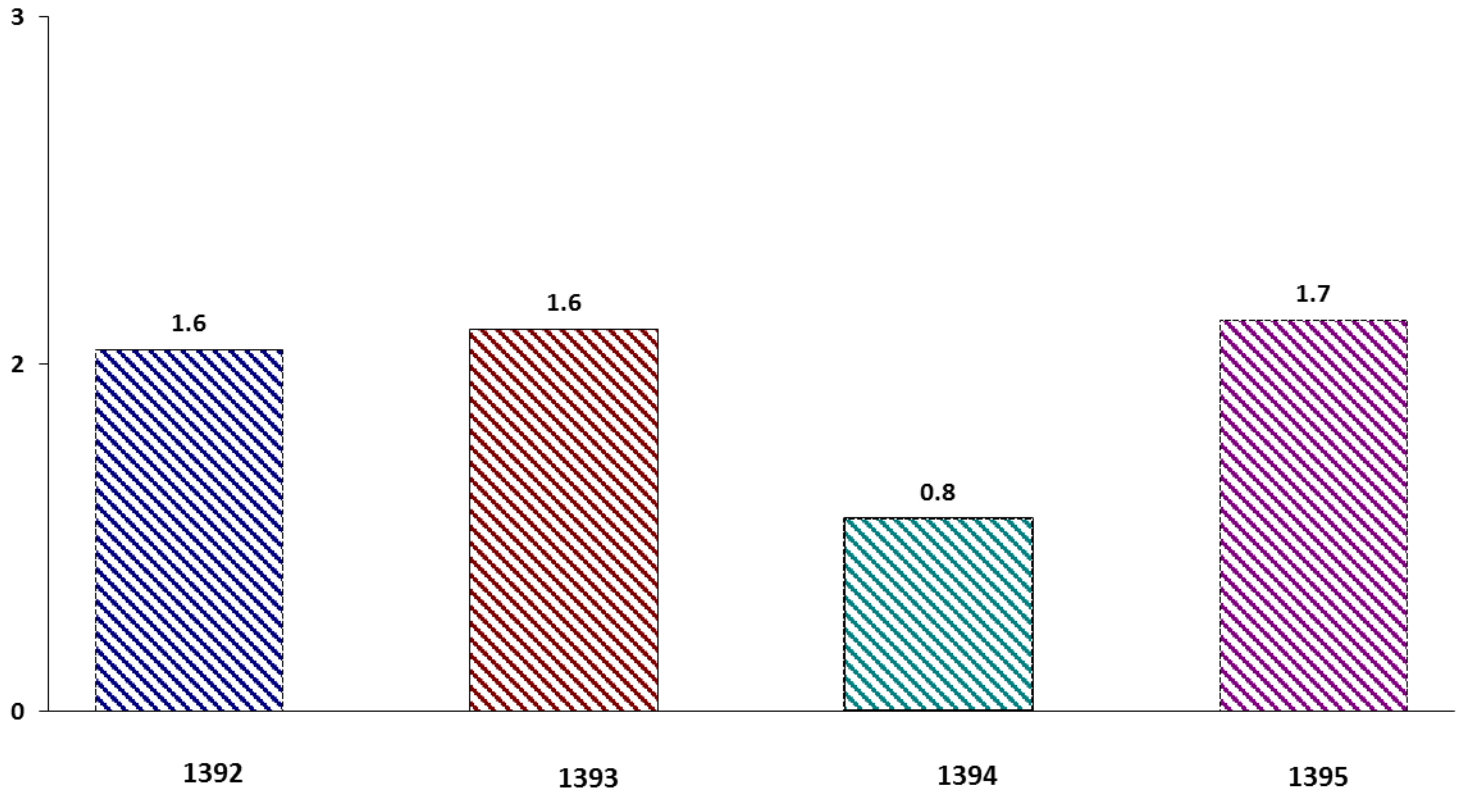
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در آذربایجان غربي (95-1392)



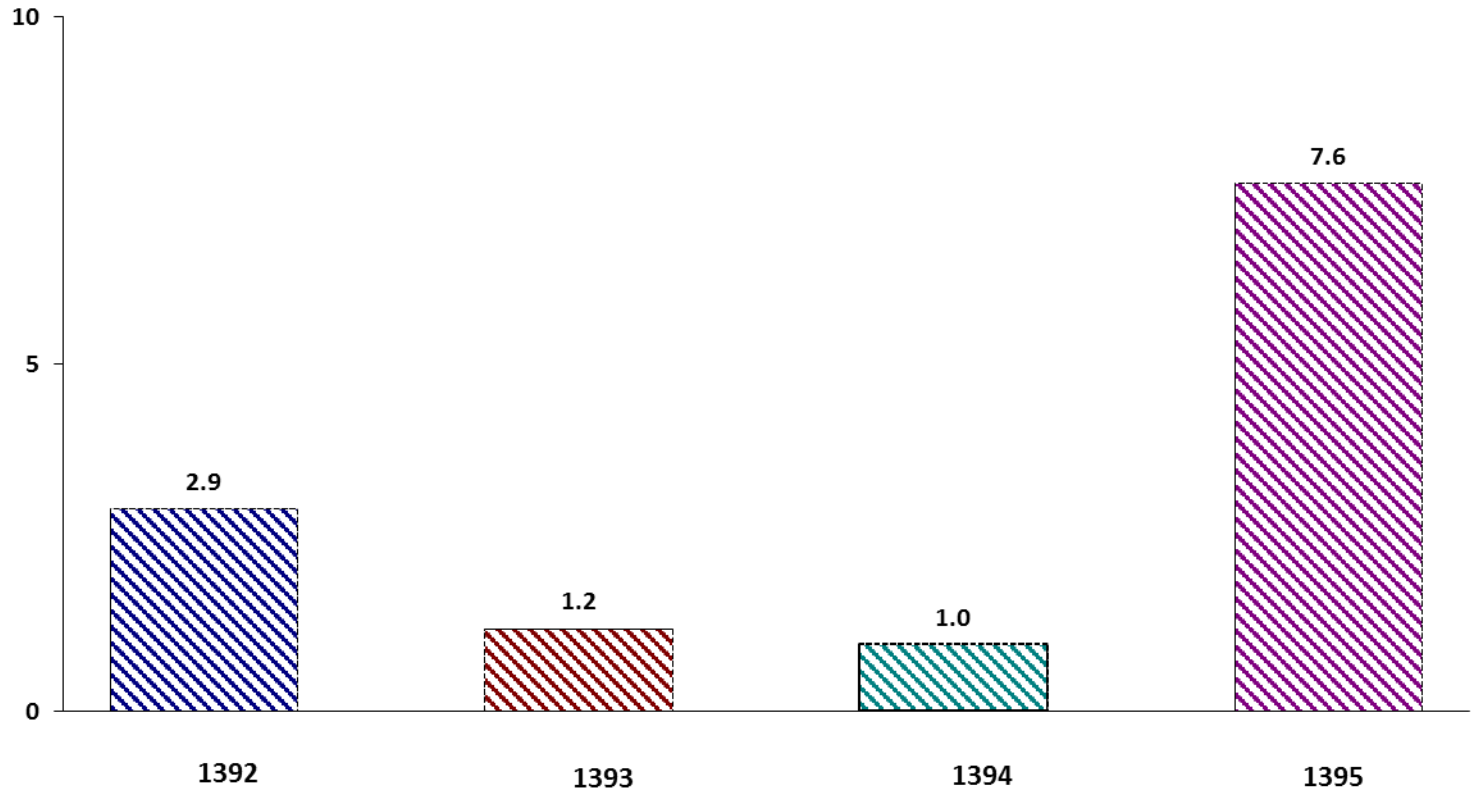
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در خراسان رضوي(95-1392)



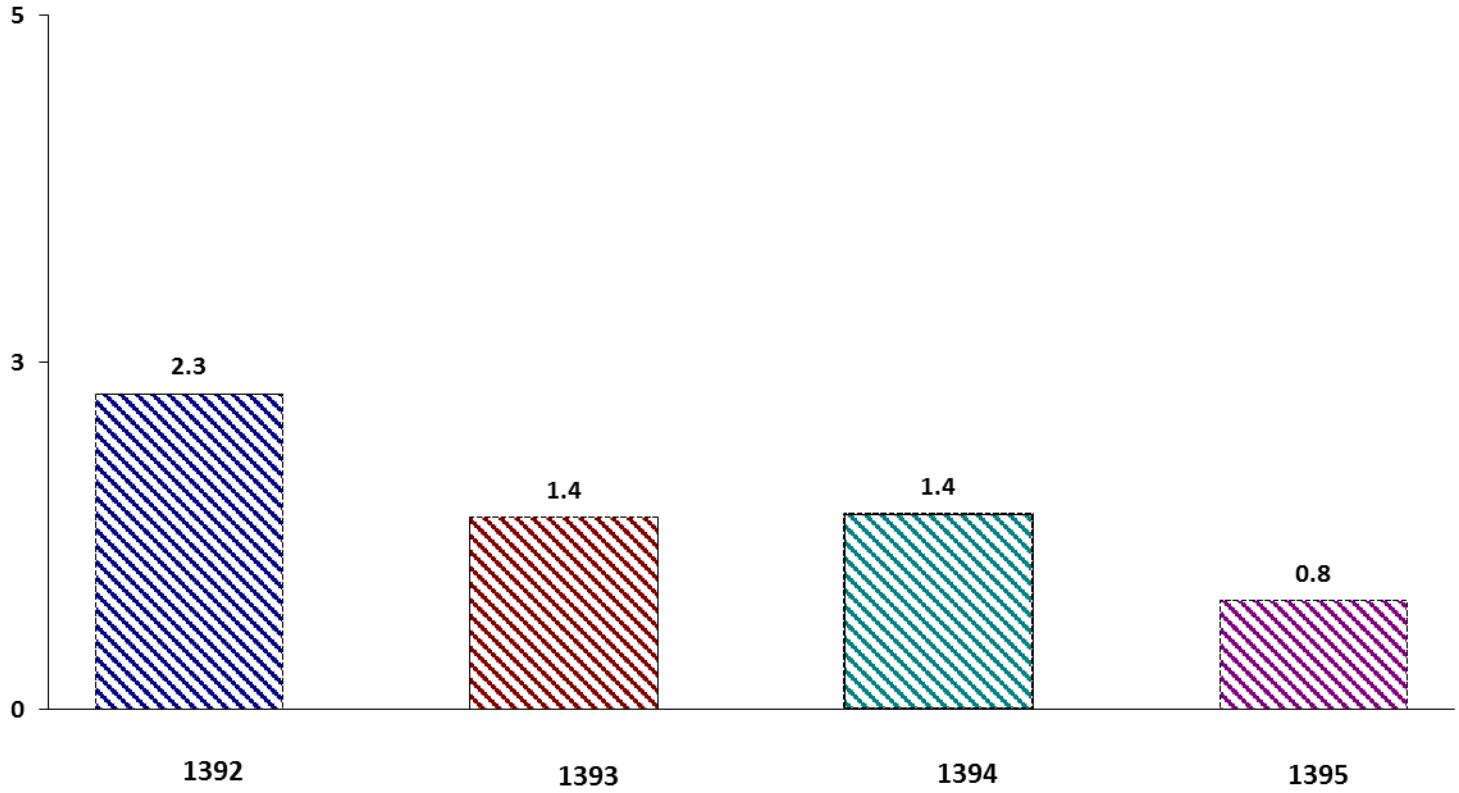
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در خراسان رضوي(95-1392)



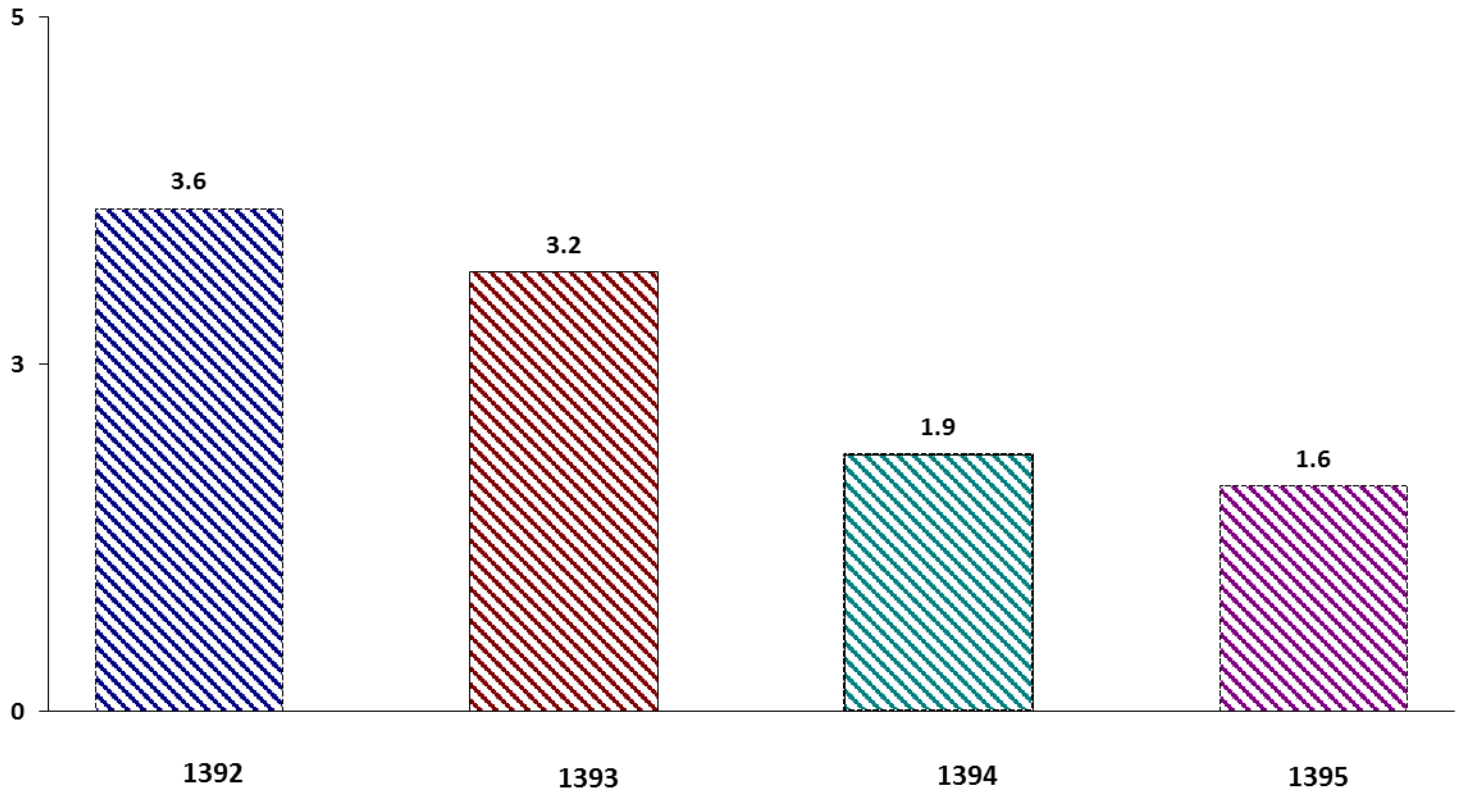
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در خراسان رضوي(95-1392)



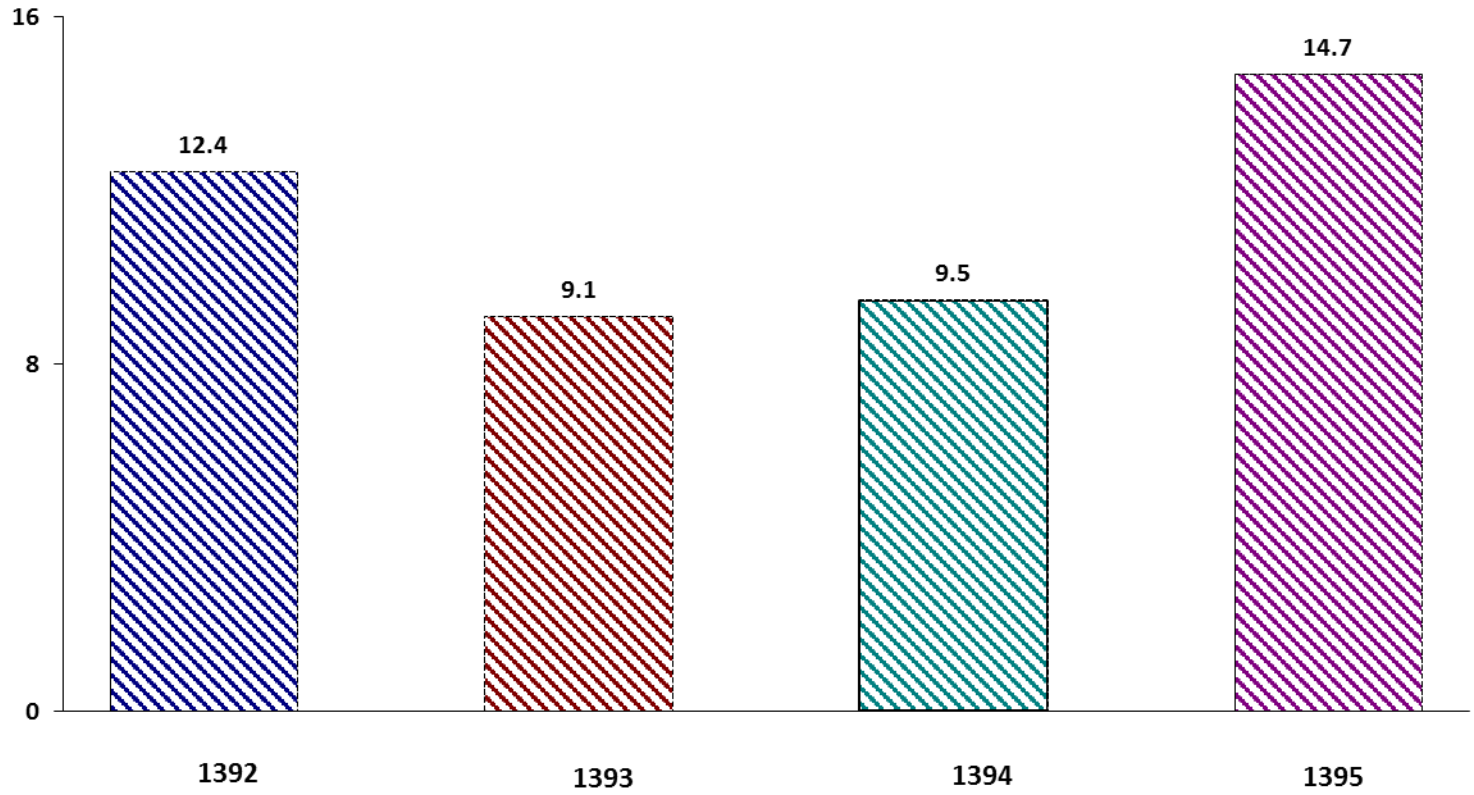
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در خراسان رضوي(95-1392)



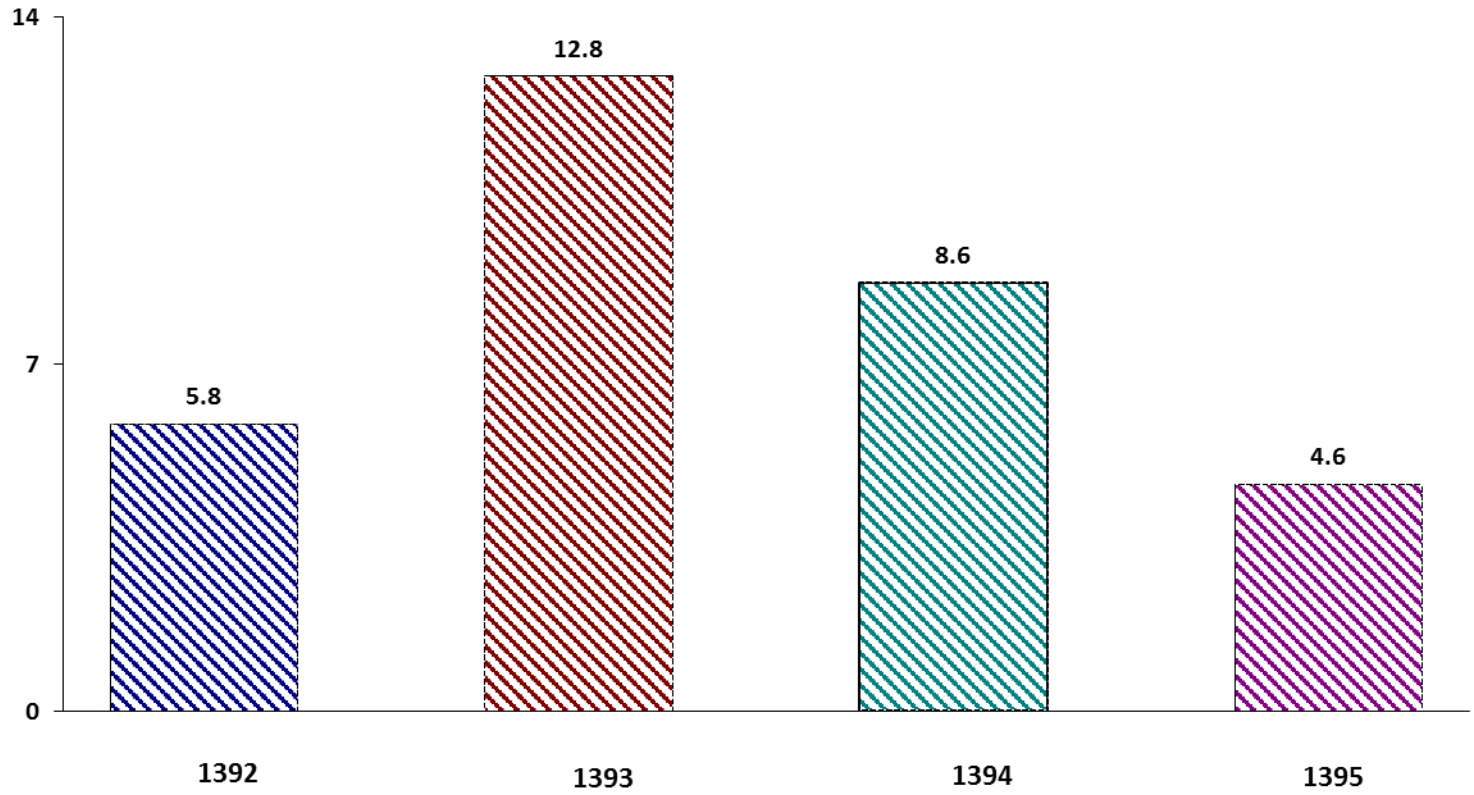
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در خراسان رضوي(95-1392)



شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در خراسان رضوي(95-1392)

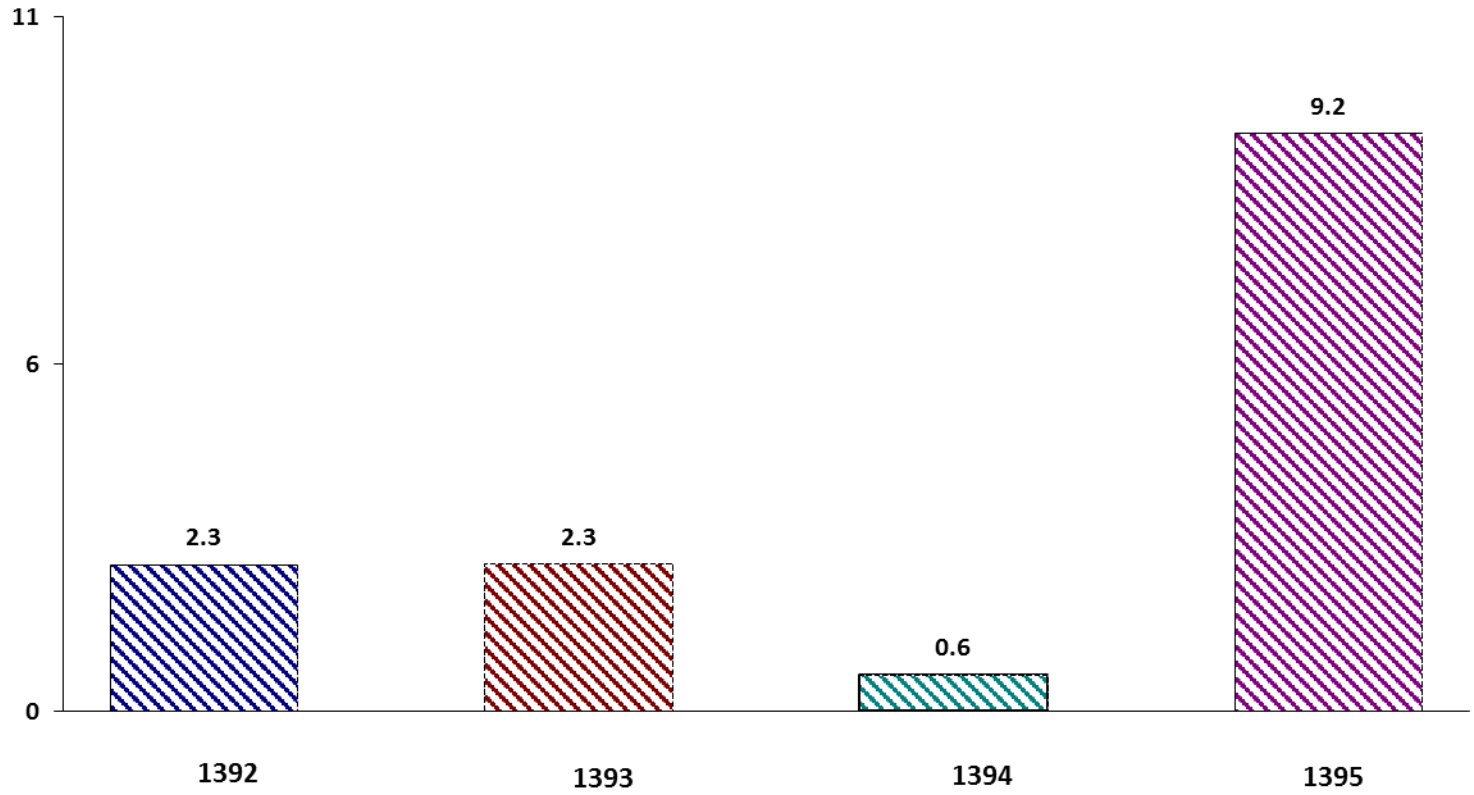


شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در خراسان شمالي(95-1392)

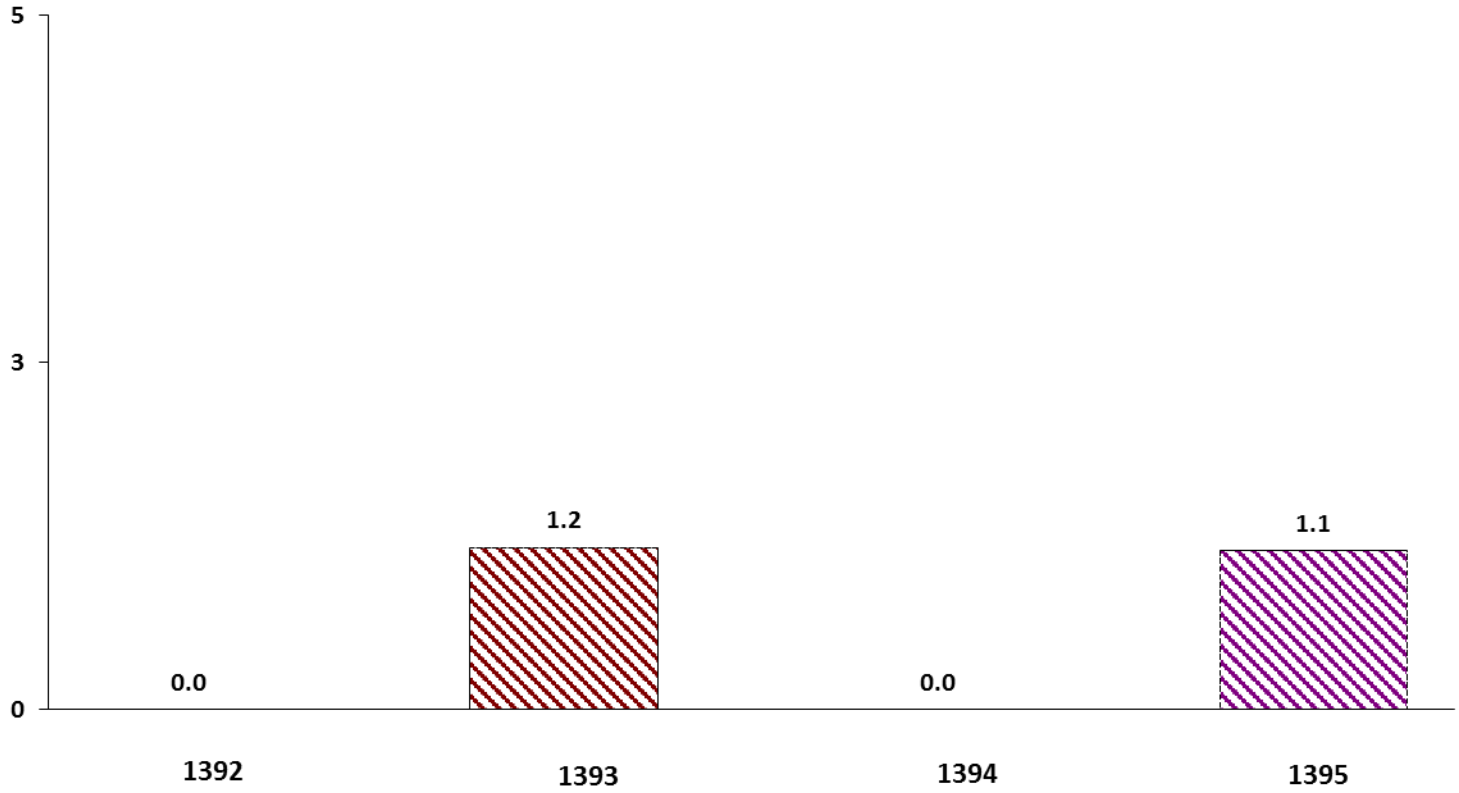


شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در خراسان شمالي(95-1392)

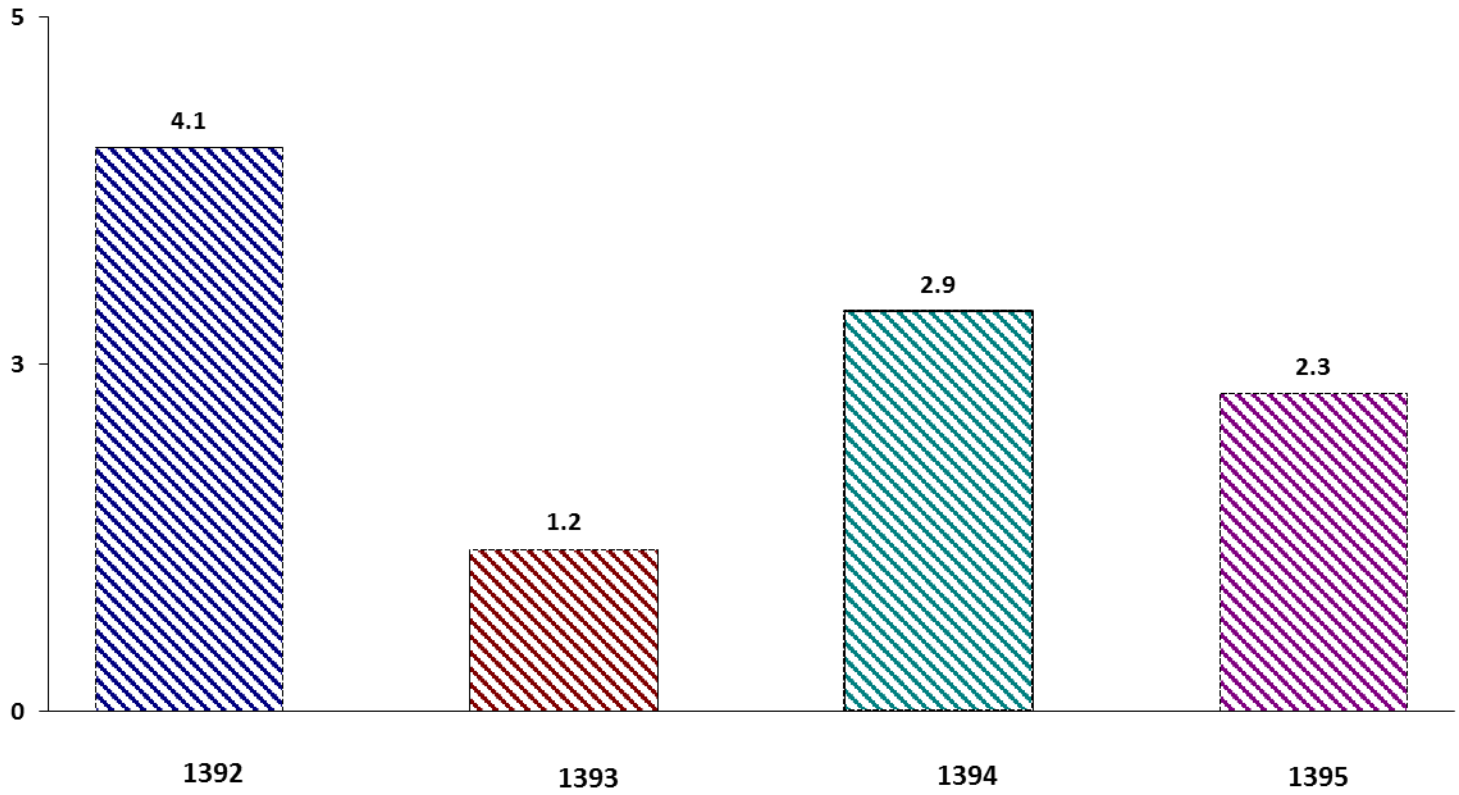
شیوع کلی ناهنجاری های مادرزادی اسکلتي و عضلاني(در هر ده هزار تولد) در خراسان شمالي(95-1392)



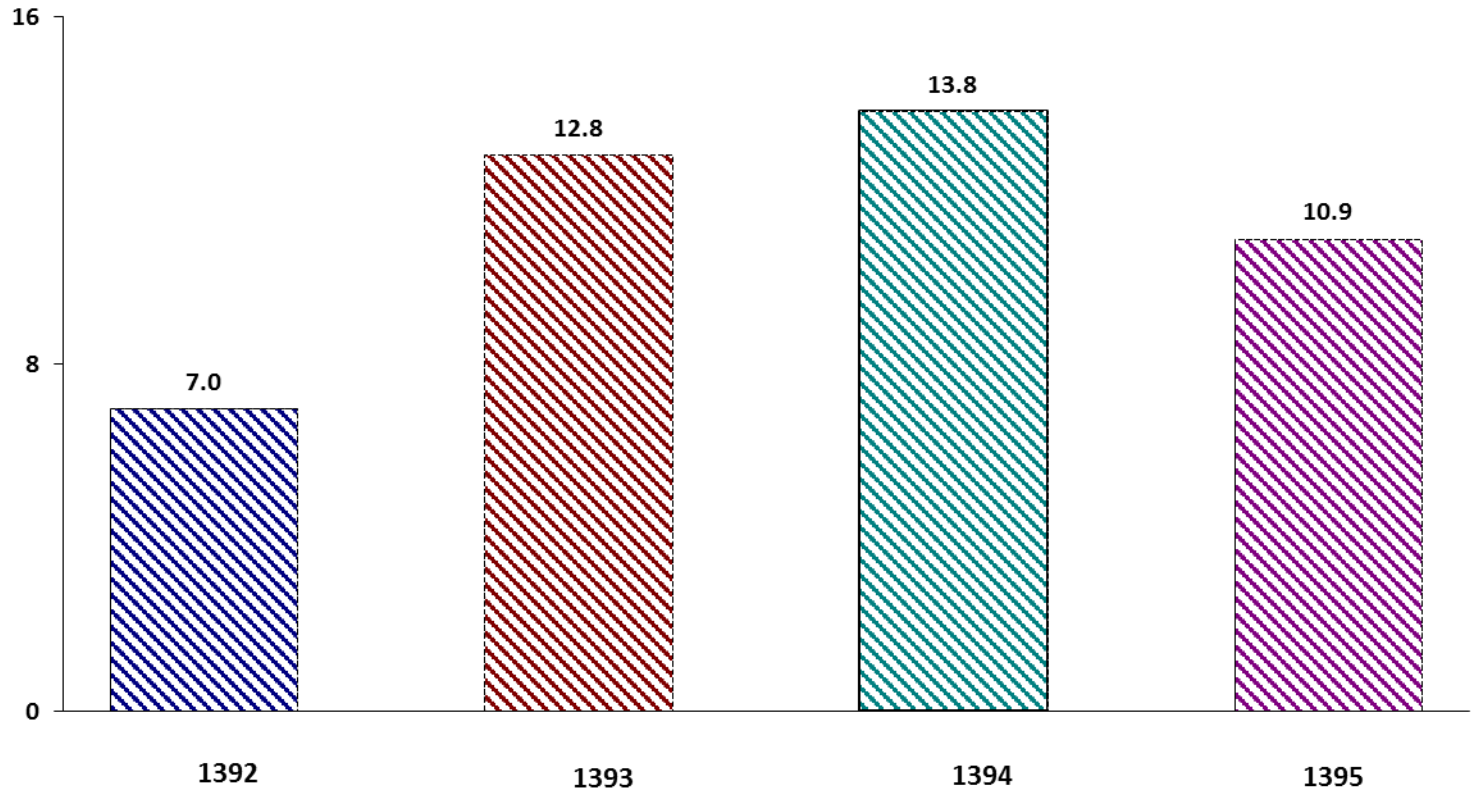
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در خراسان شمالي(95-1392)



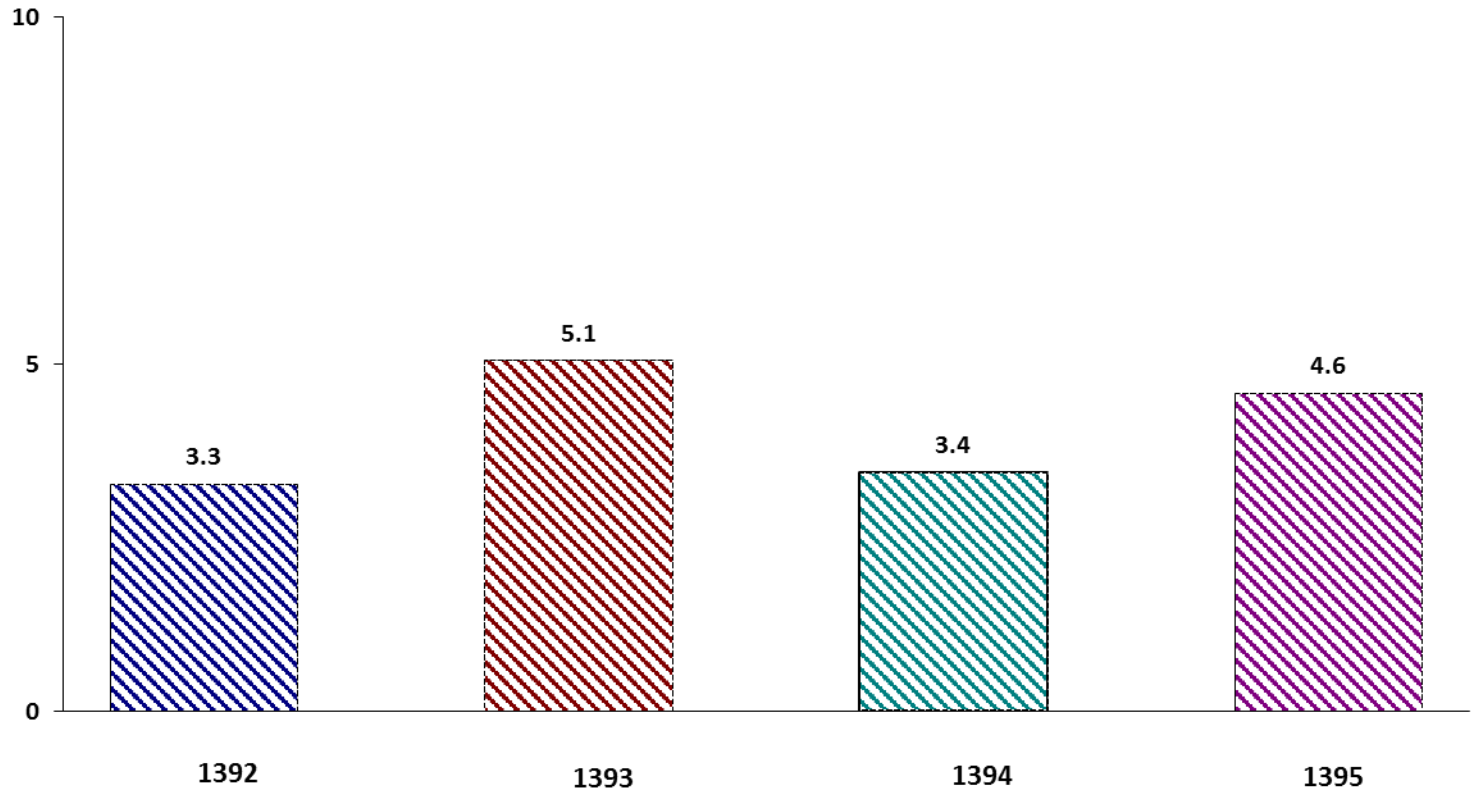
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در خراسان شمالي(95-1392)



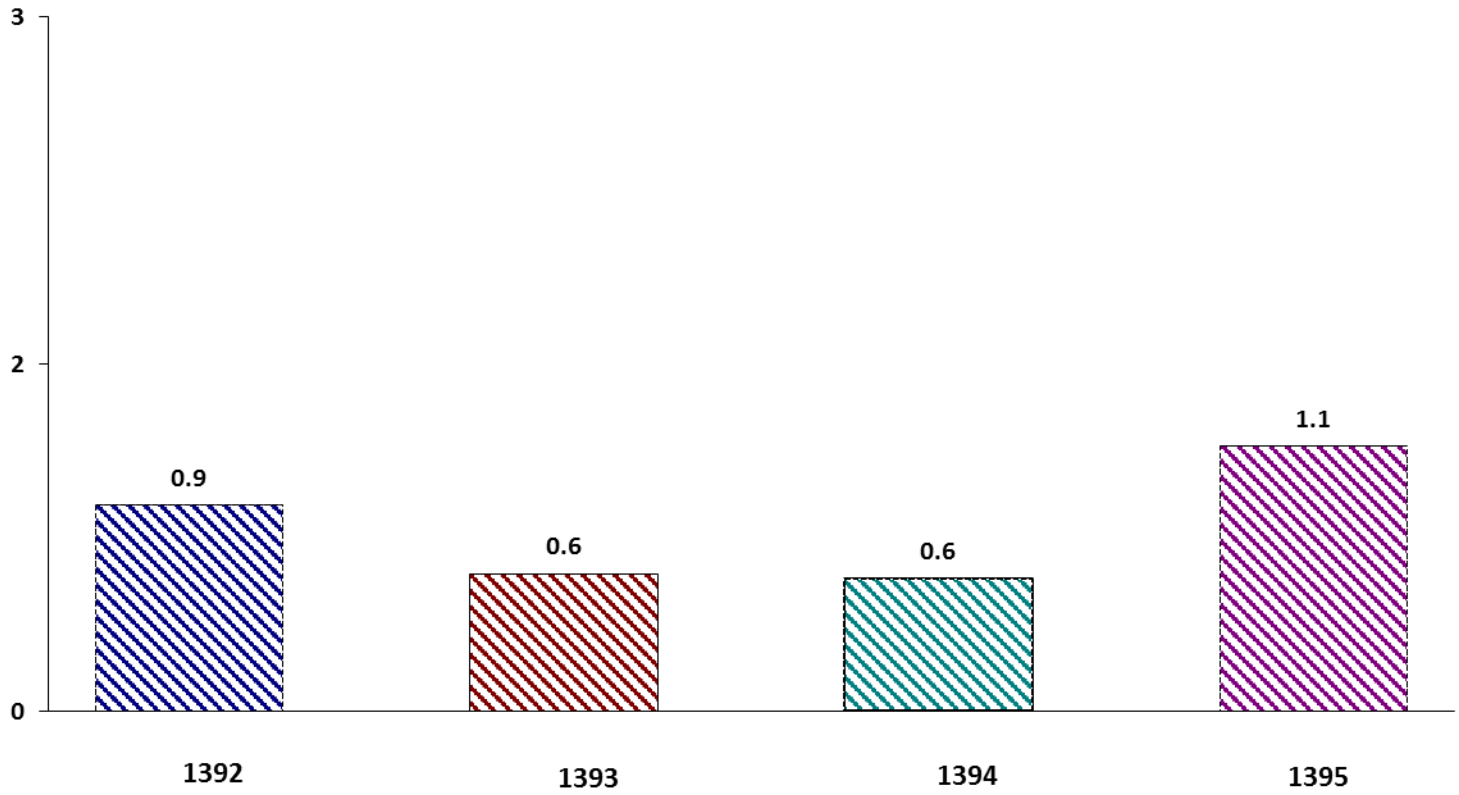
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در خراسان شمالي(95-1392)



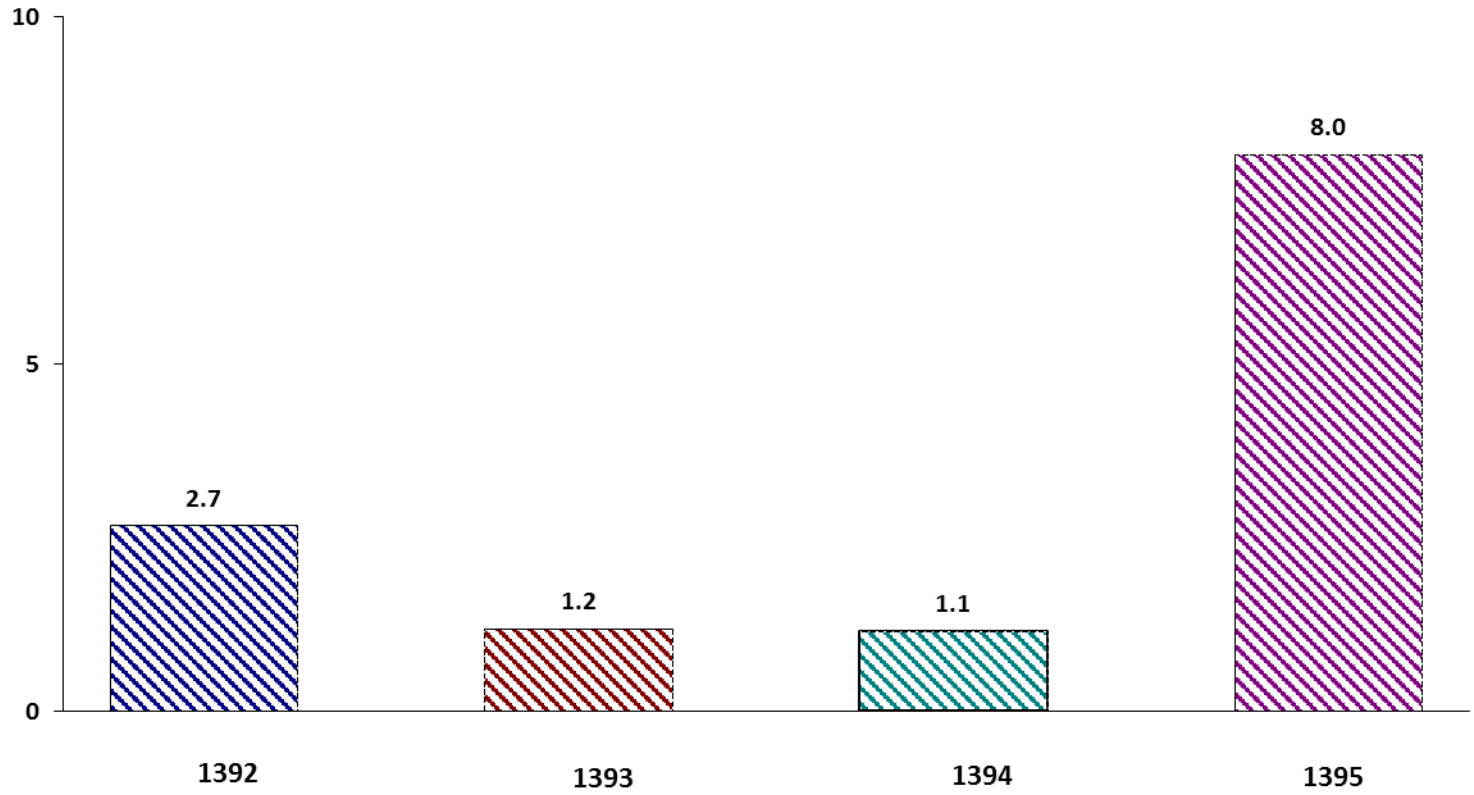
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درکرمانشاه(95-1392)



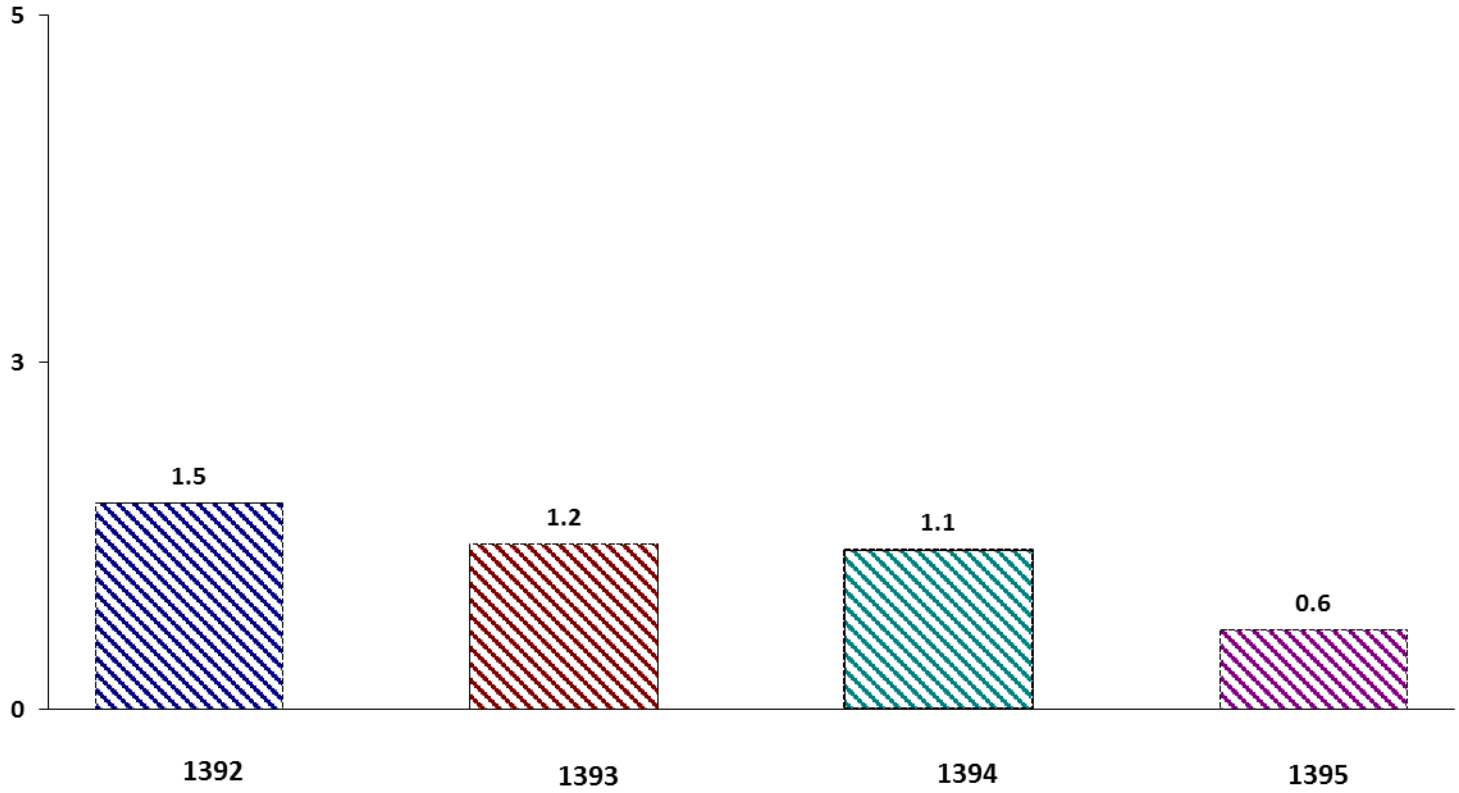
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درکرمانشاه(95-1392)



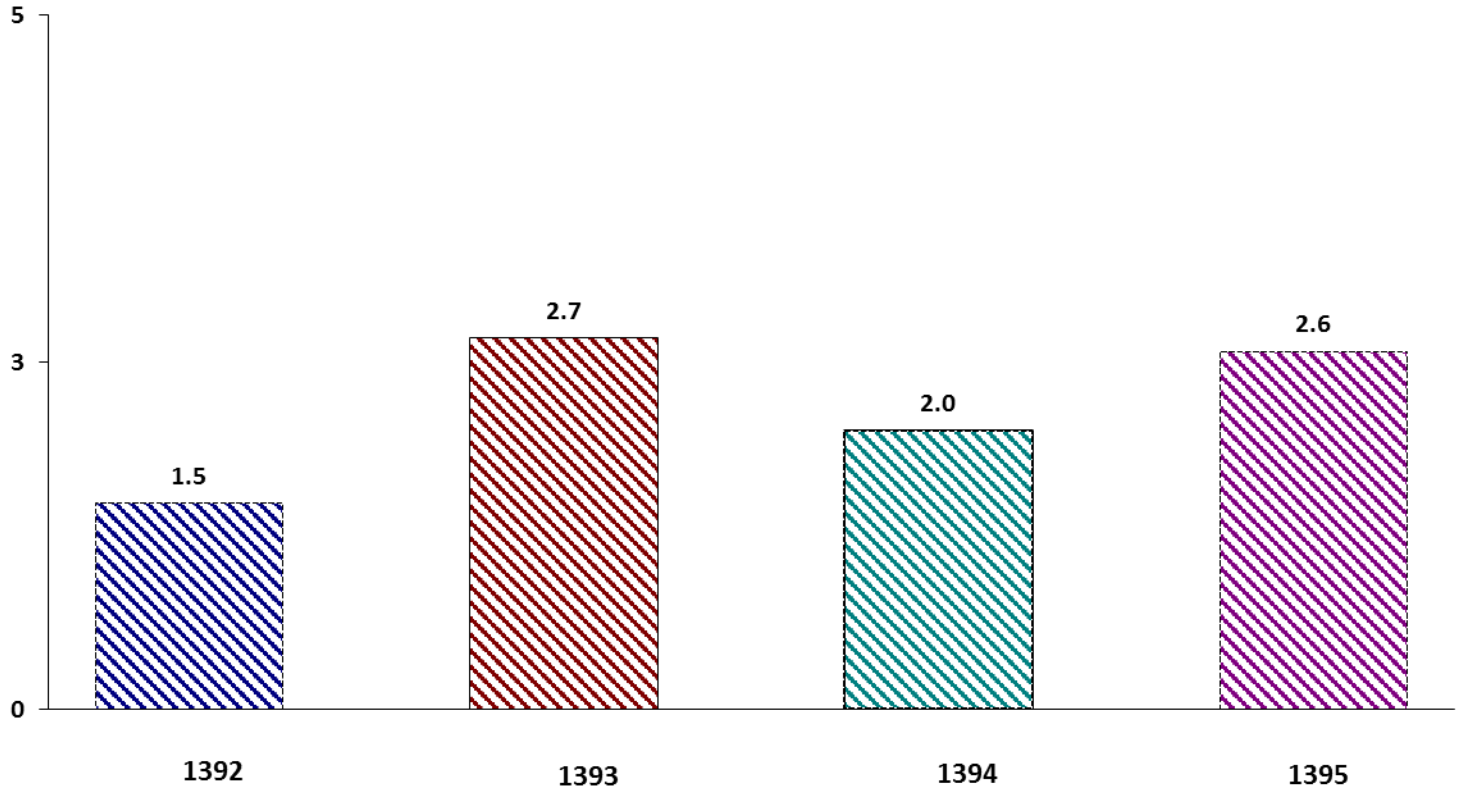
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درکرمانشاه(95-1392)



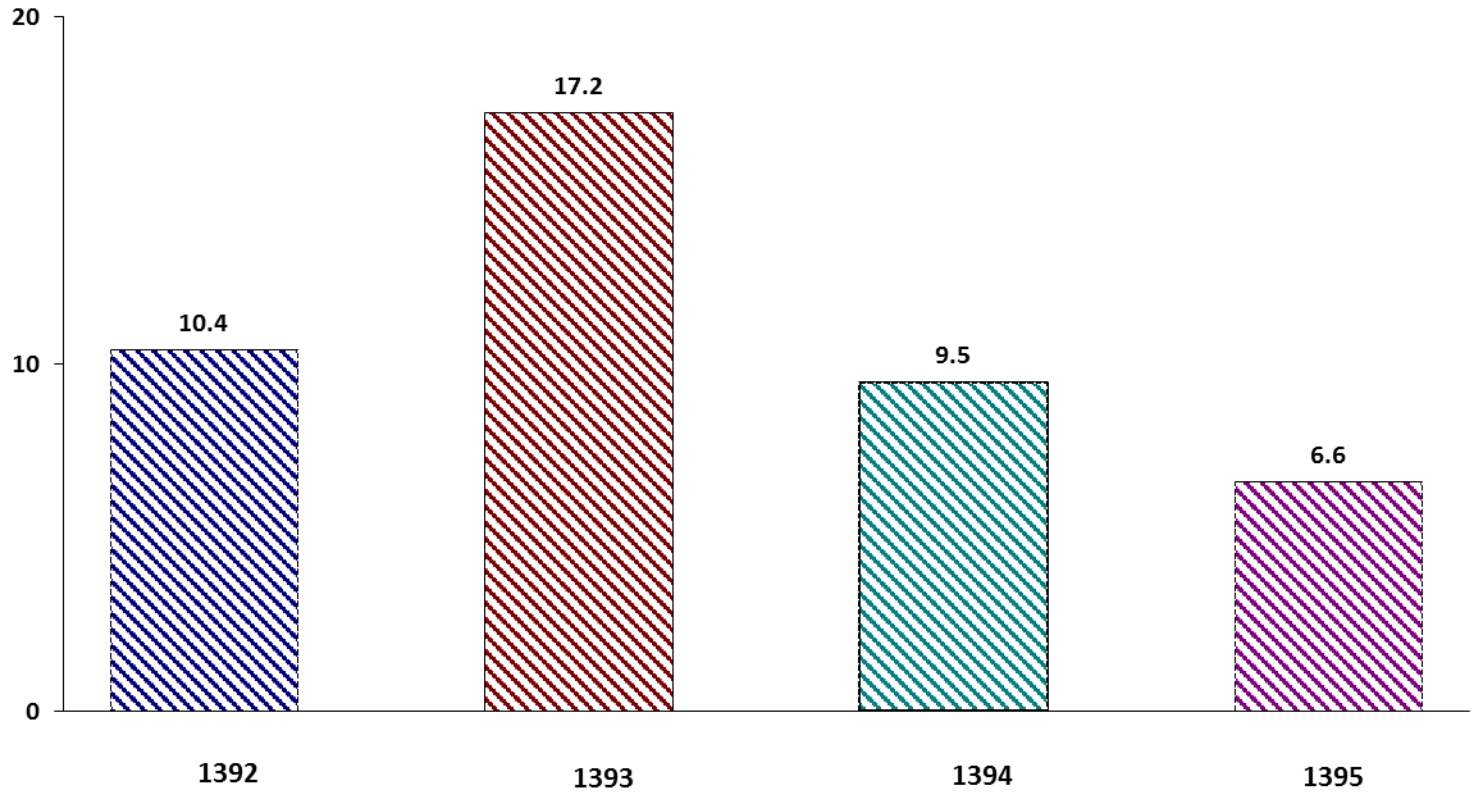
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درکرمانشاه(95-1392)



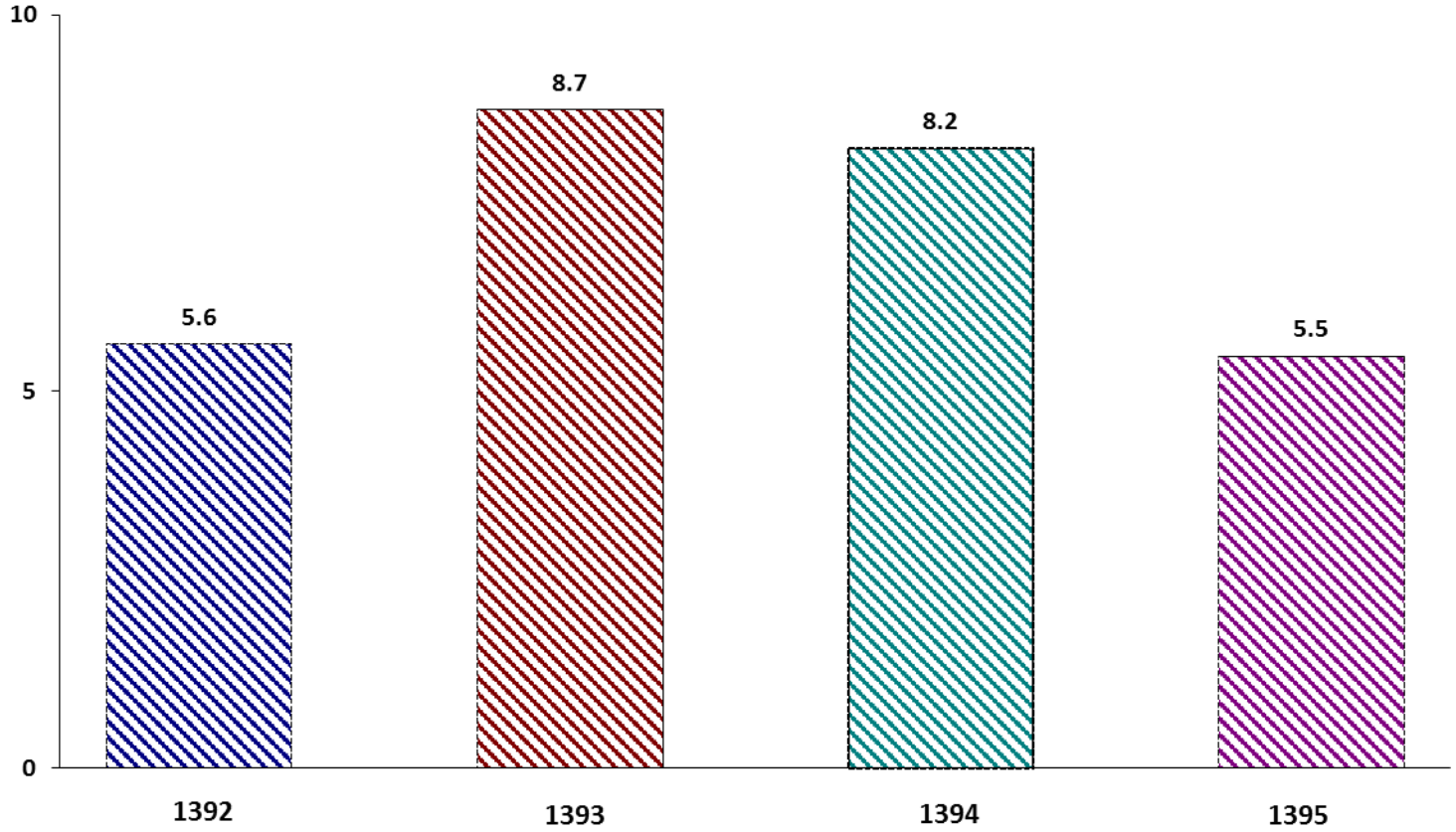
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درکرمانشاه(95-1392)



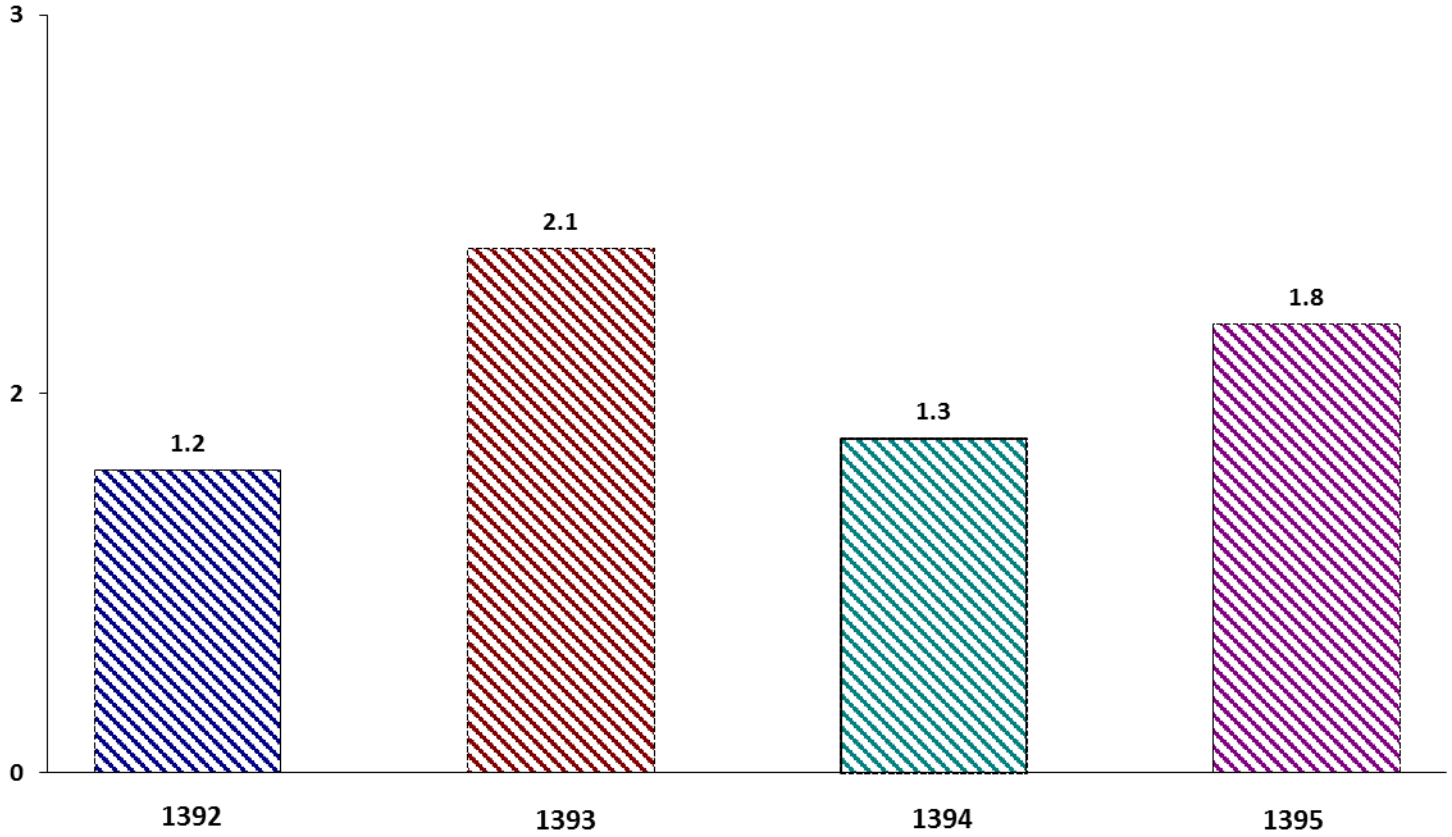
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درکرمانشاه(95-1392)



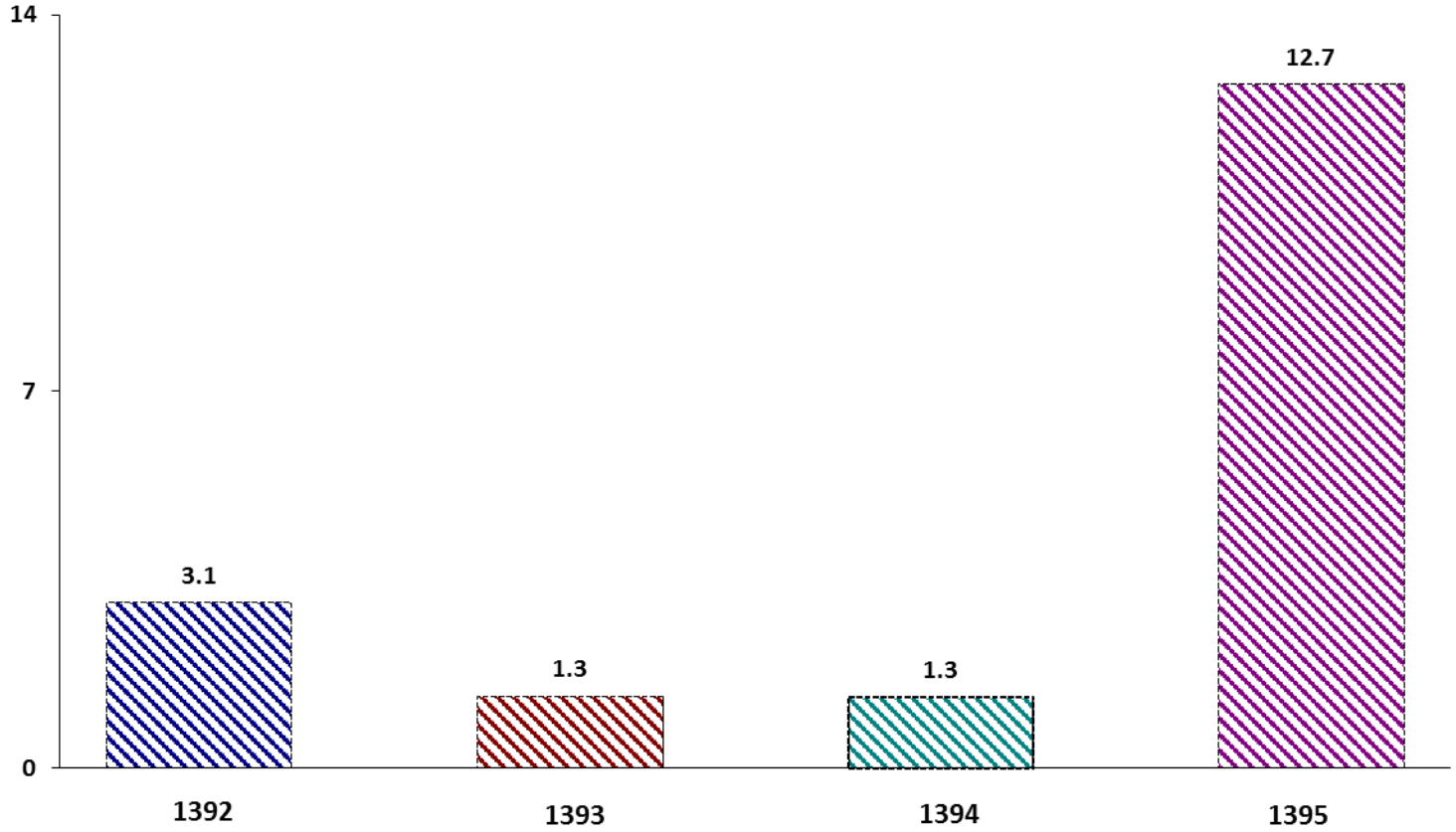
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در آذربایجان شرقي(95 -1392)



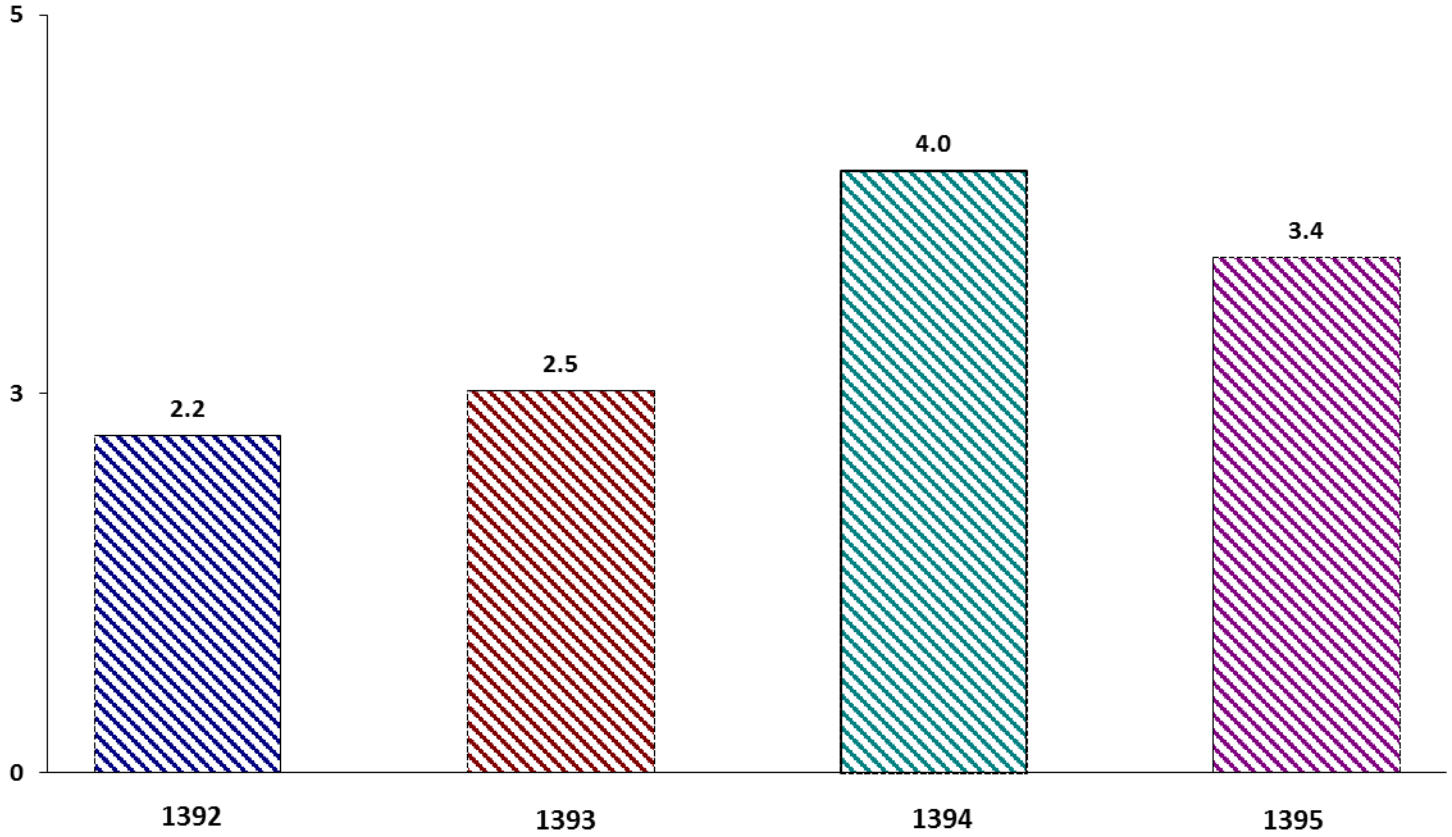
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در آذربایجان شرقي(95 -1392)



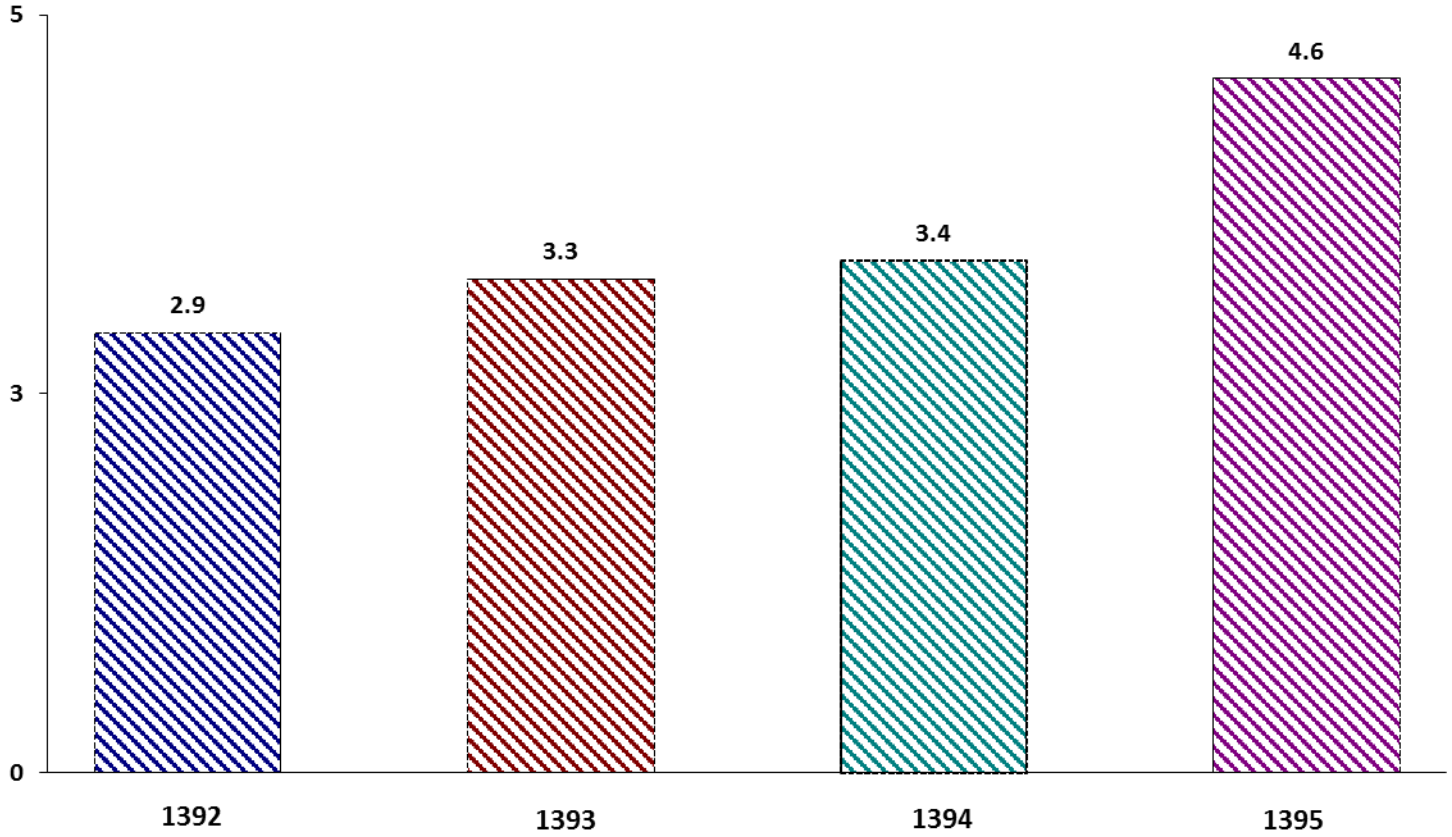
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در آذربایجان شرقي(95 -1392)



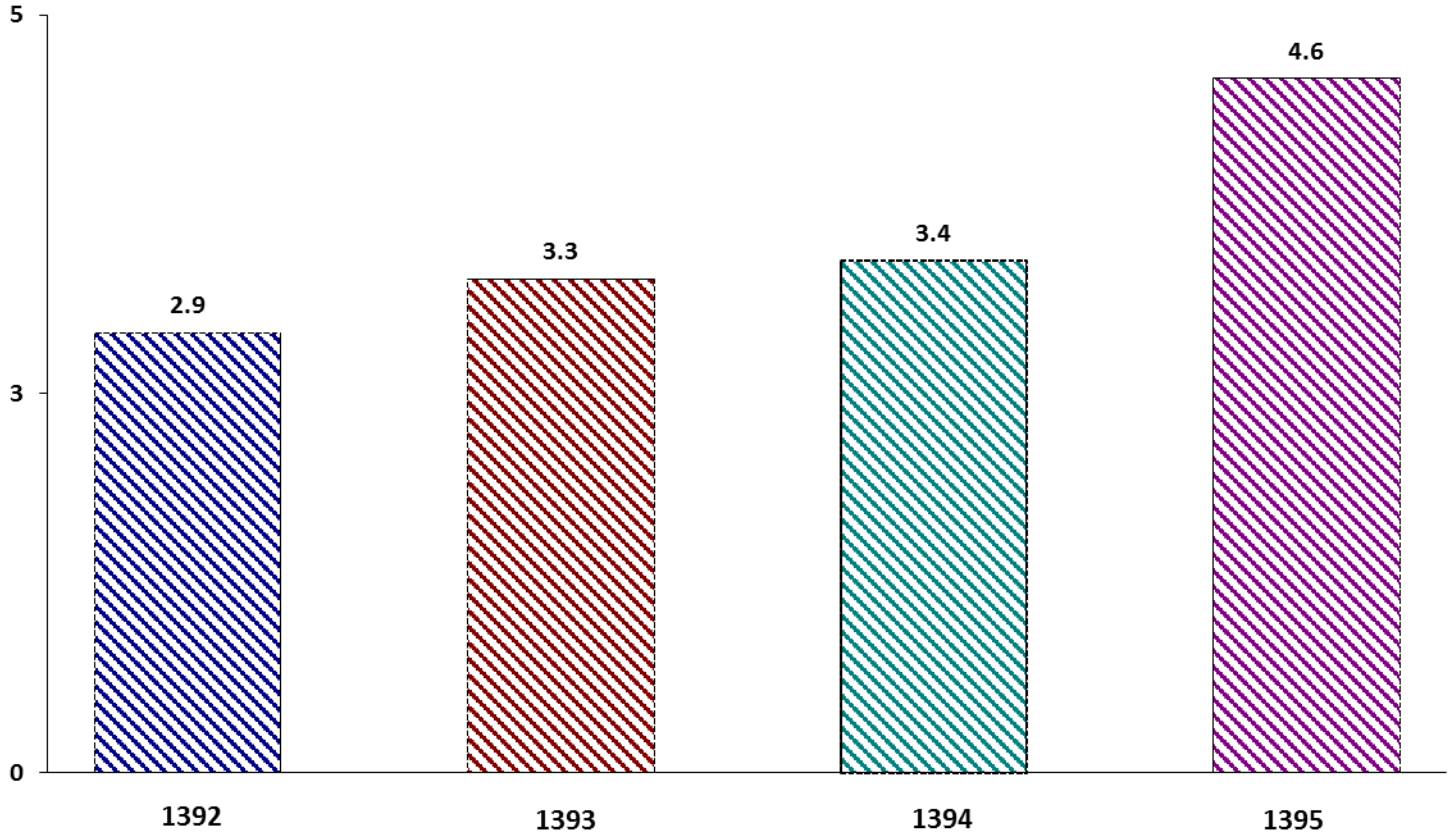
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در آذربایجان شرقي(95 -1392)



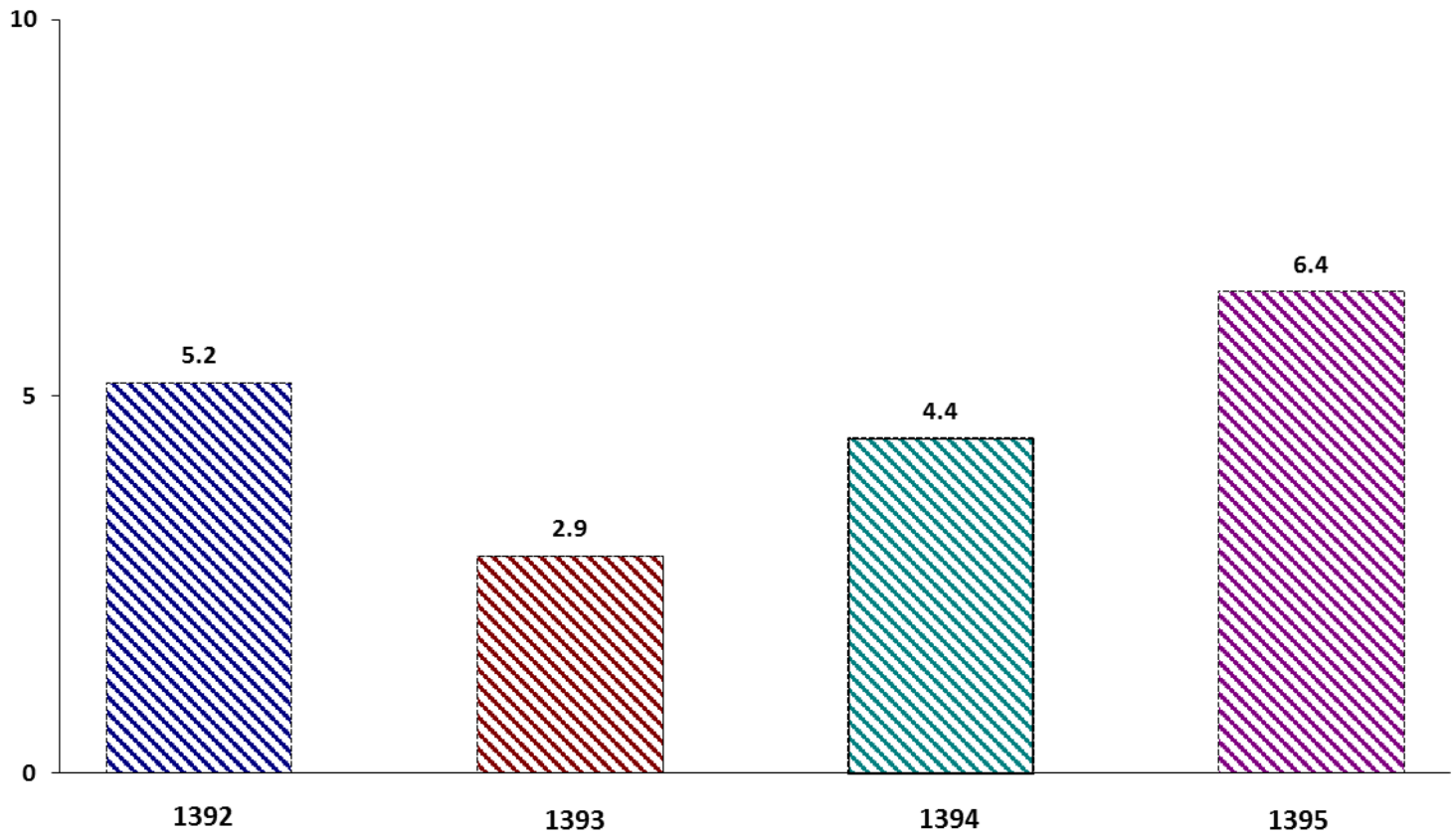
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در آذربایجان شرقي(95 -1392)



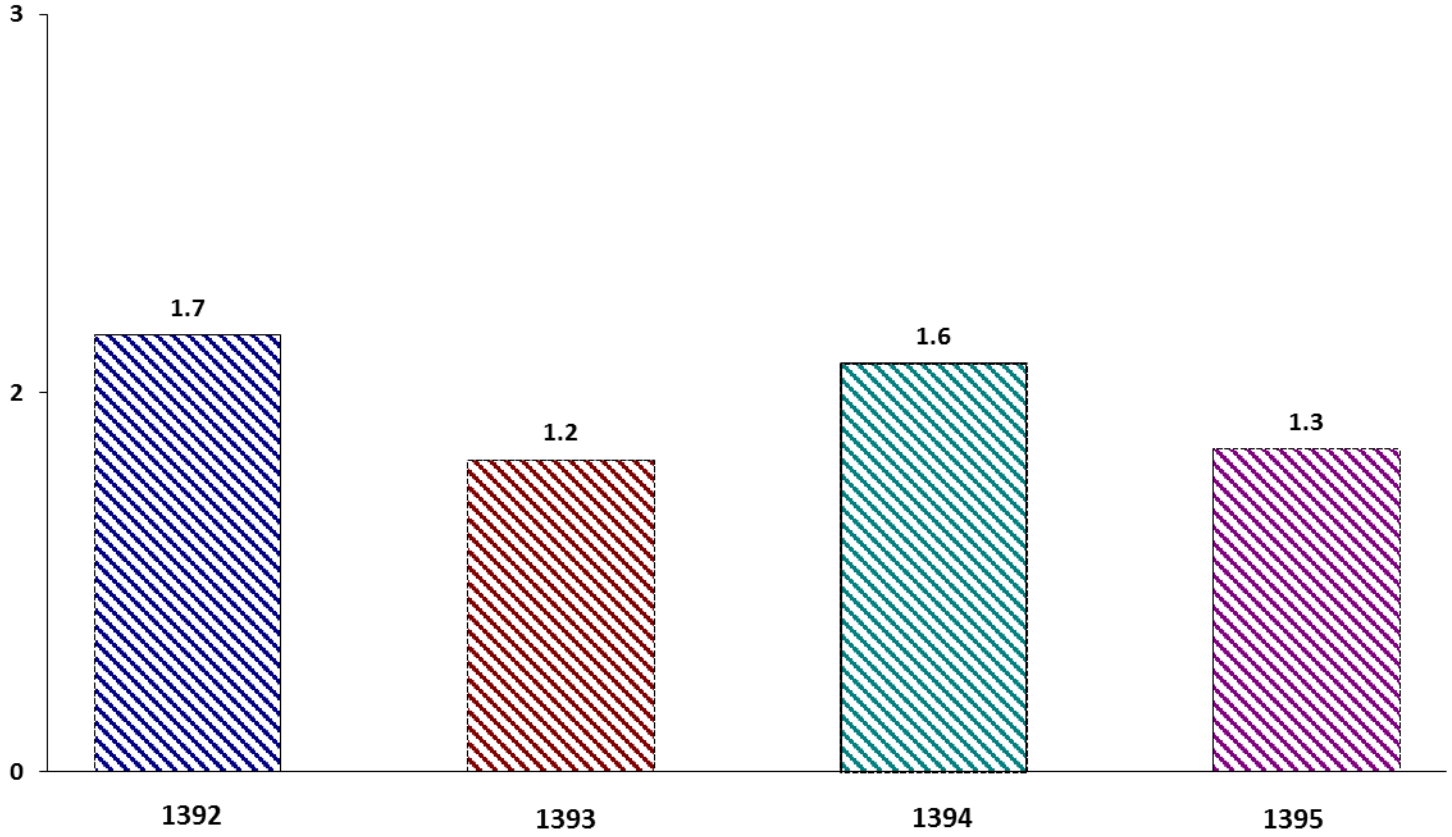
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در آذربایجان شرقي(95 -1392)



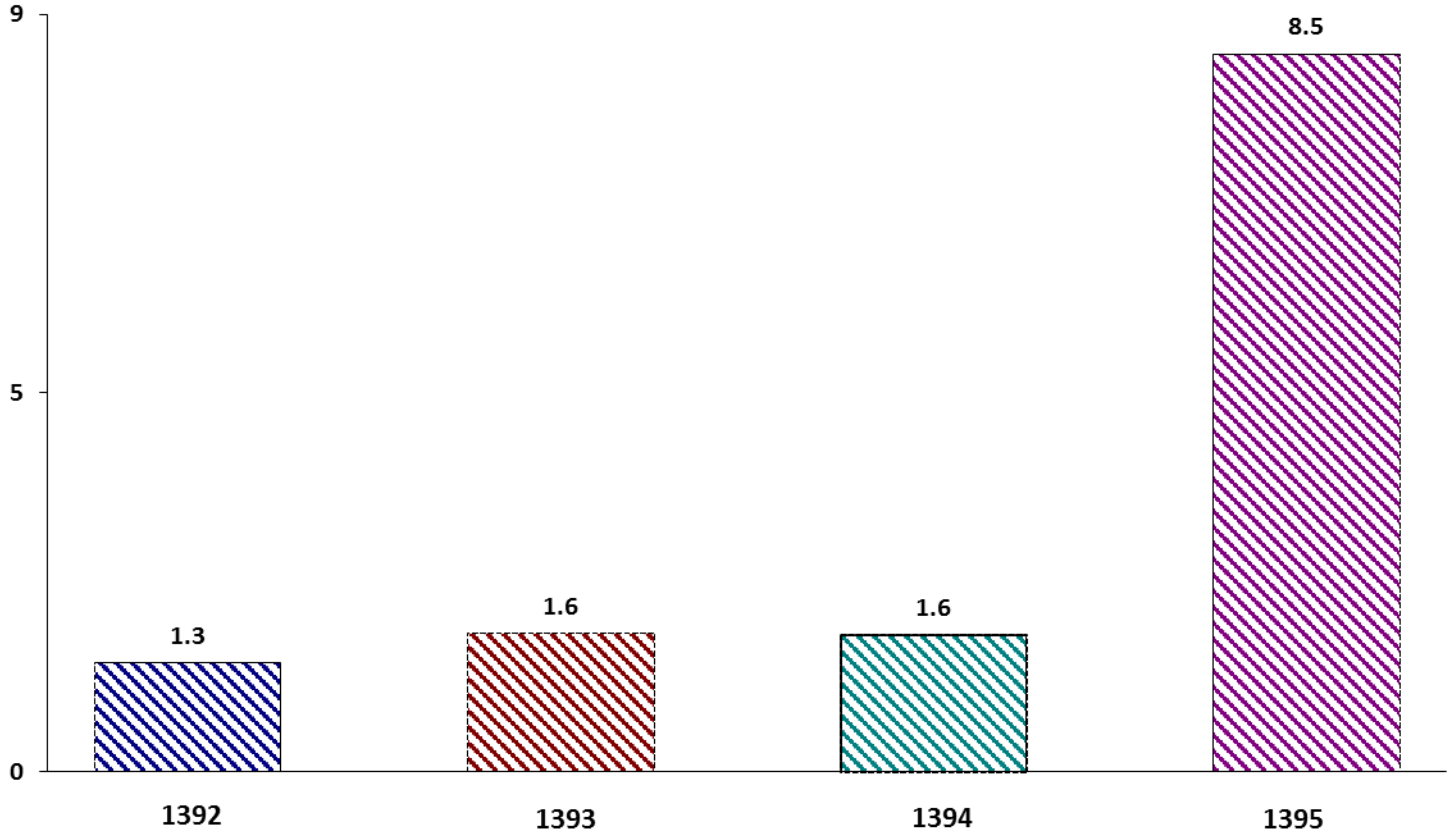
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در اردبیل(95-1392)



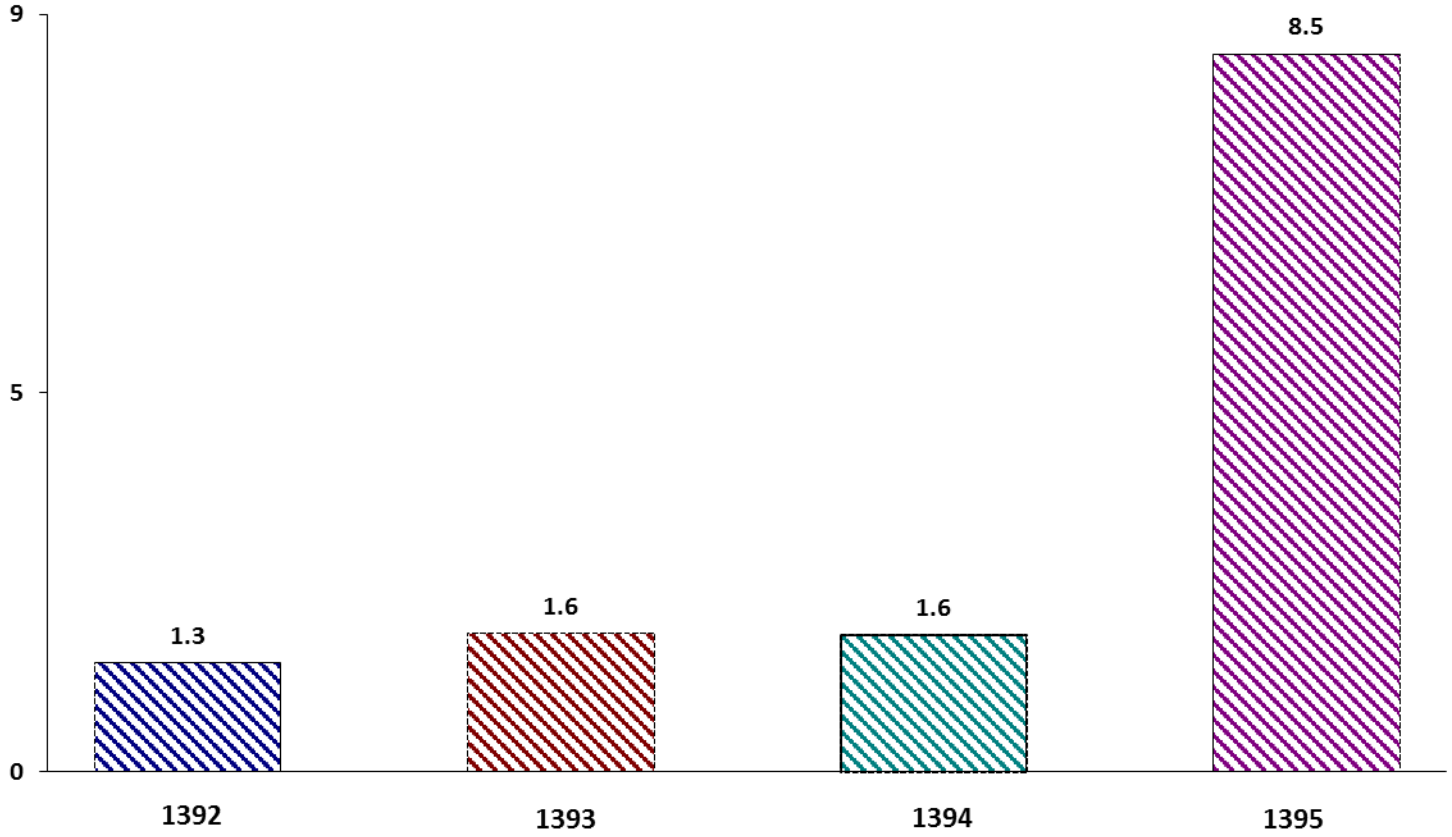
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در اردبیل(95-1392)



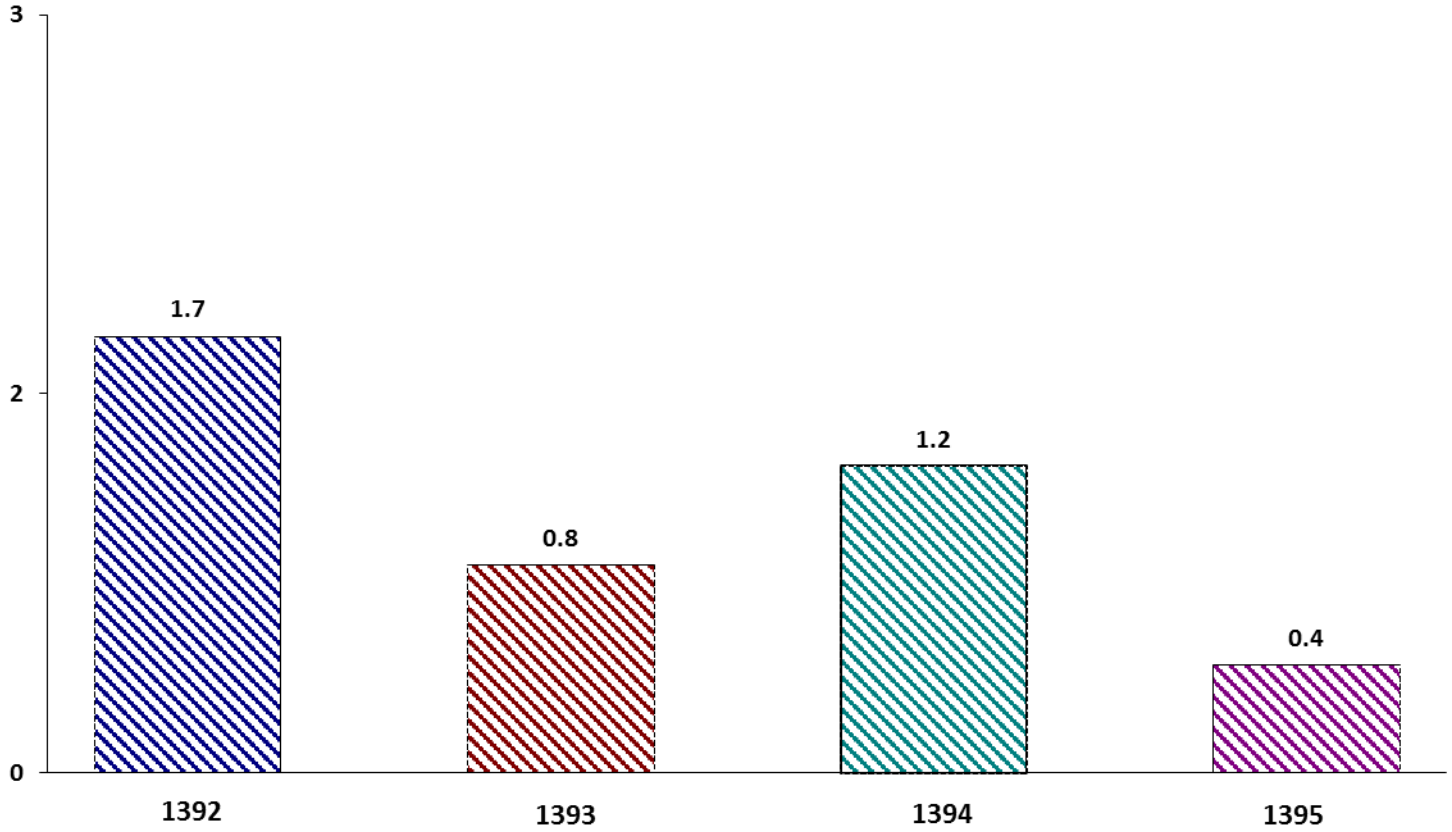
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در اردبیل(95-1392)



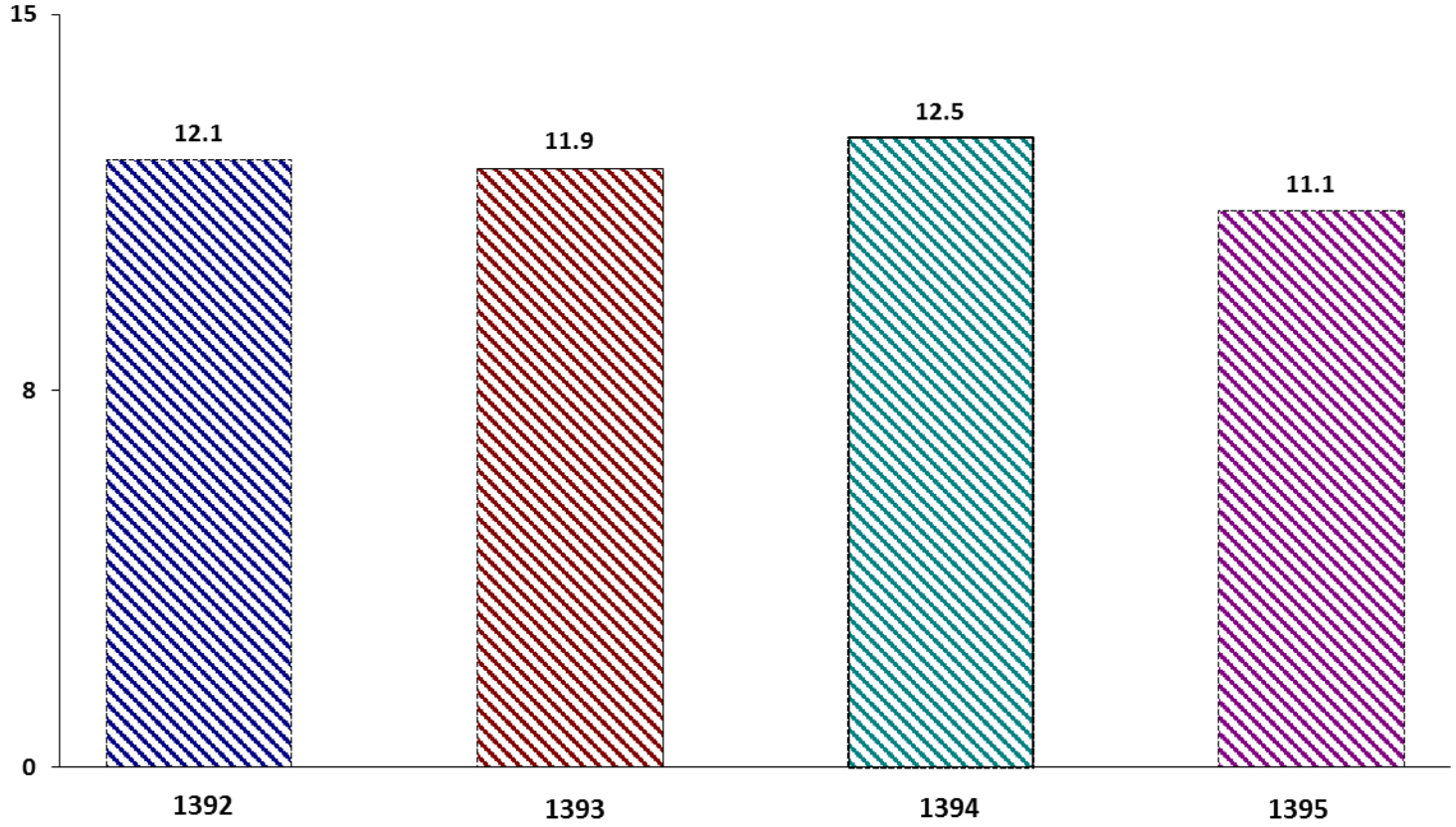
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در اردبیل(95-1392)



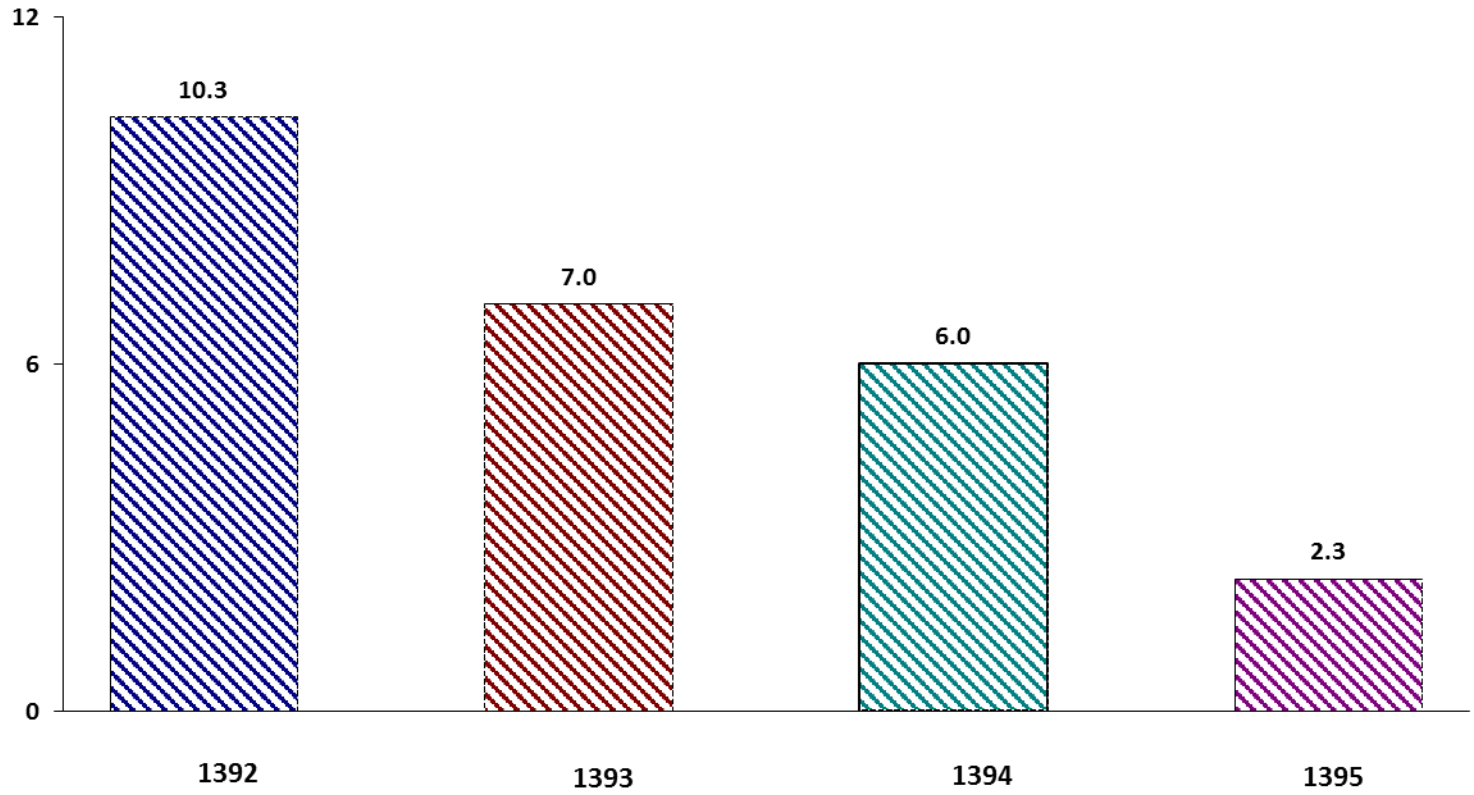
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در اردبیل(95-1392)



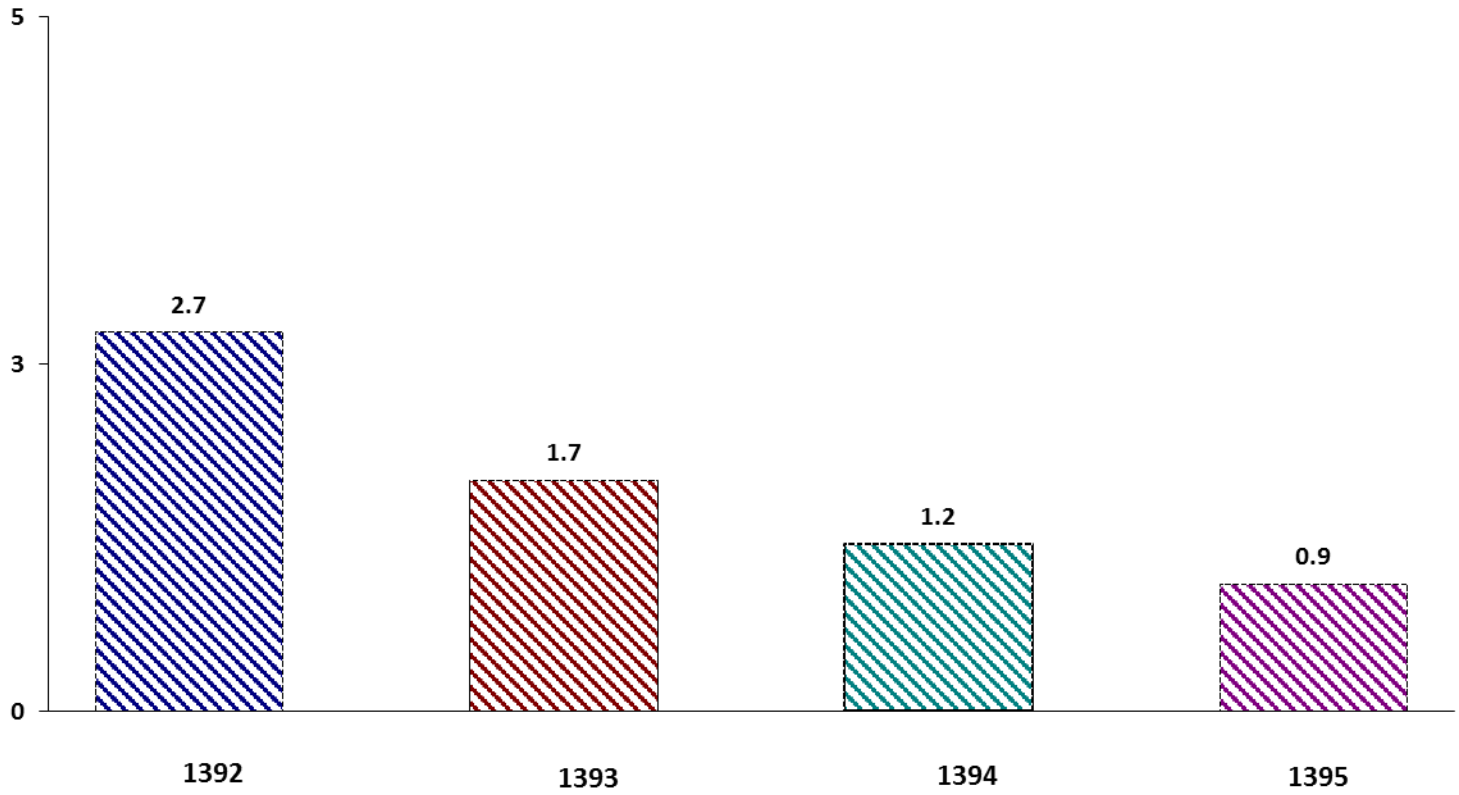
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در اردبیل(95-1392)



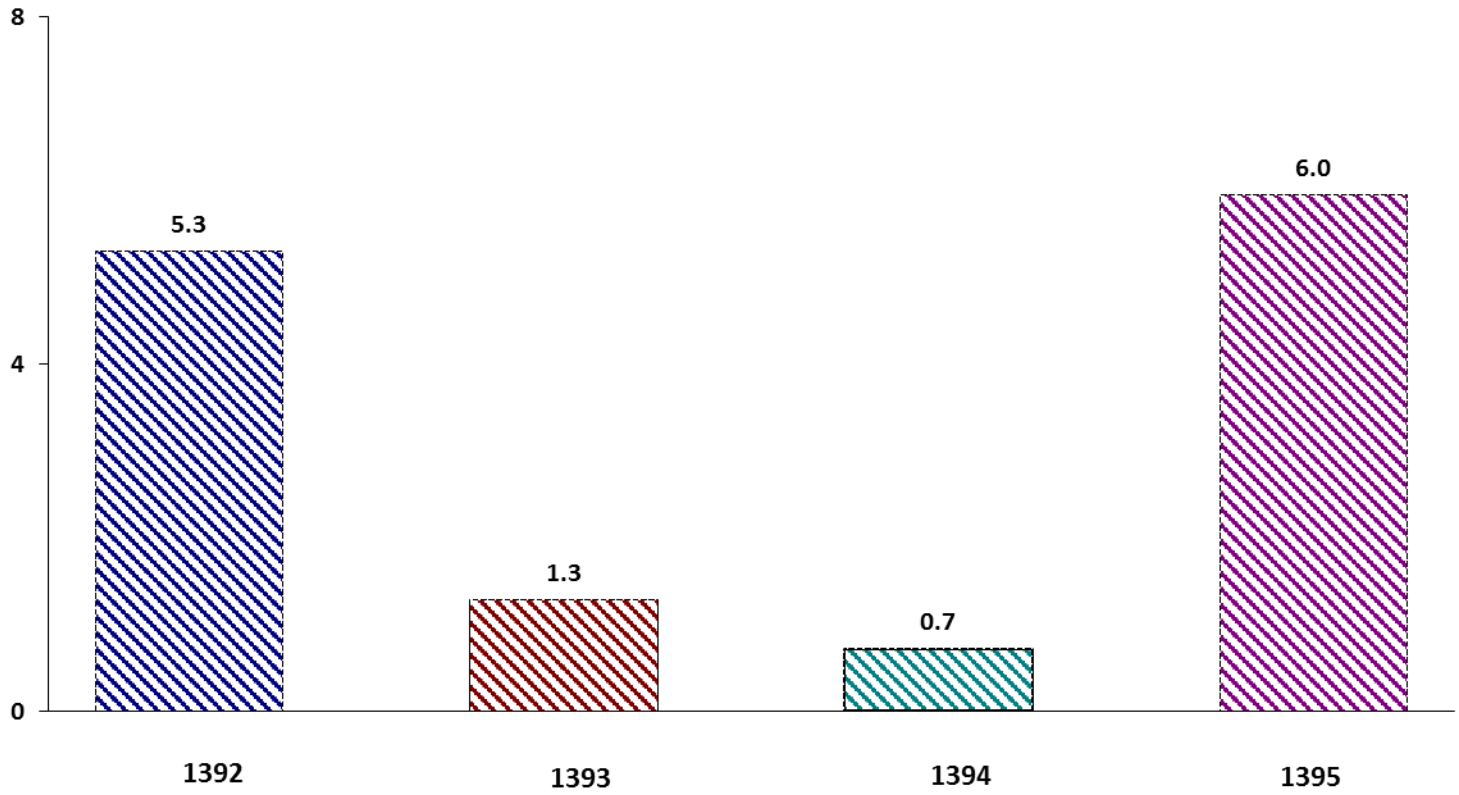
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در اصفهان(95-1392)



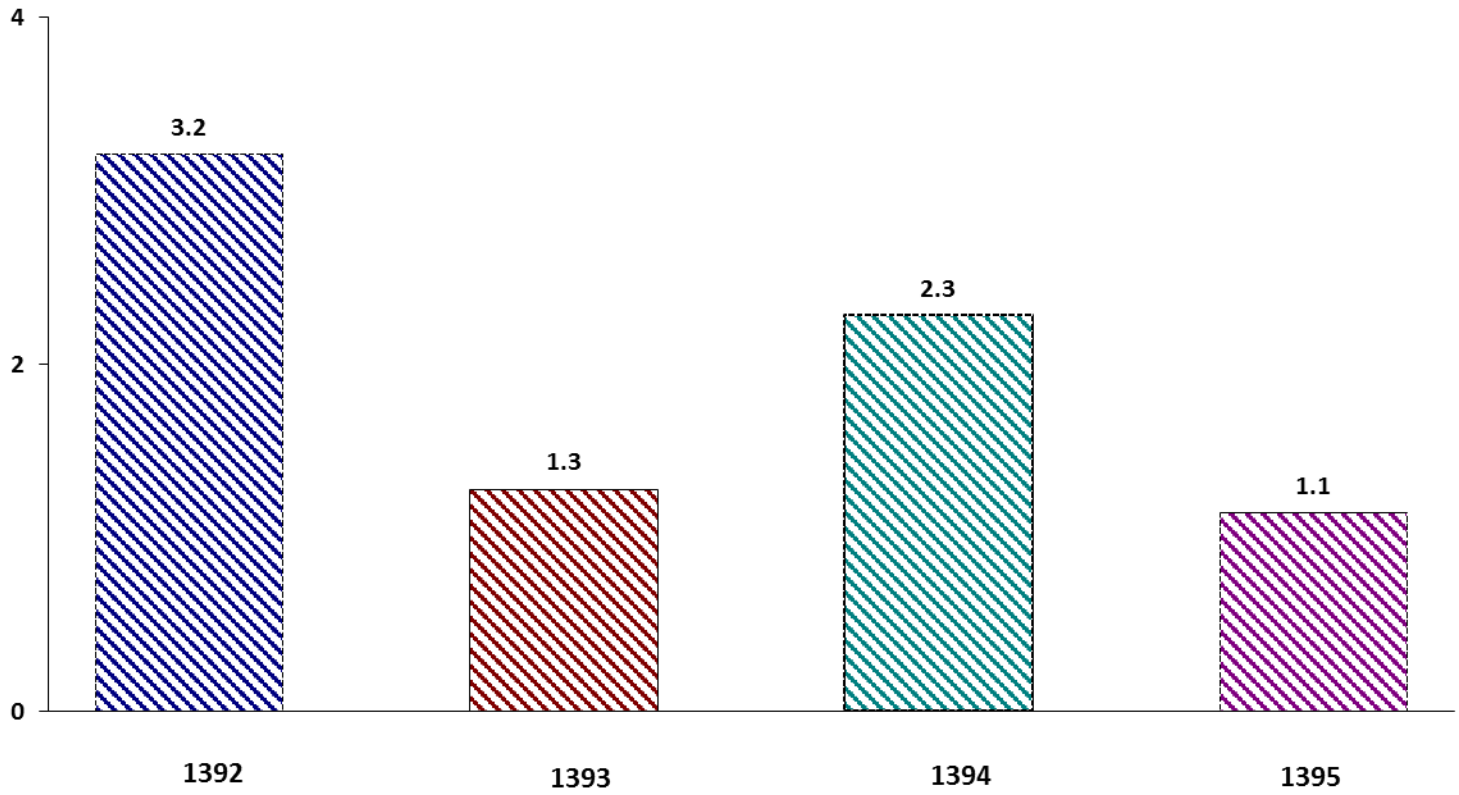
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در اصفهان(95-1392)



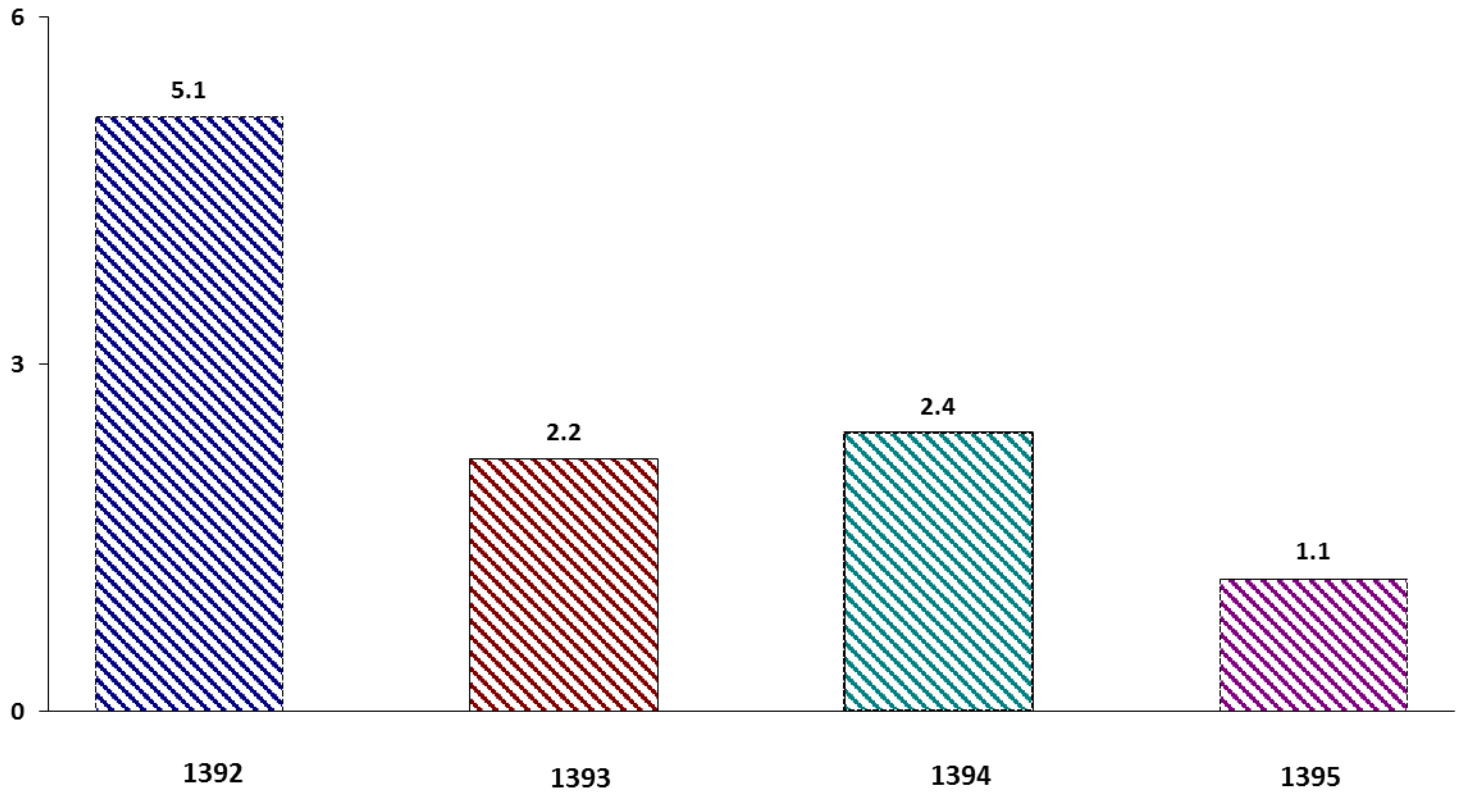
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسكلتي(در هر ده هزار تولد) در اصفهان(95-1392)



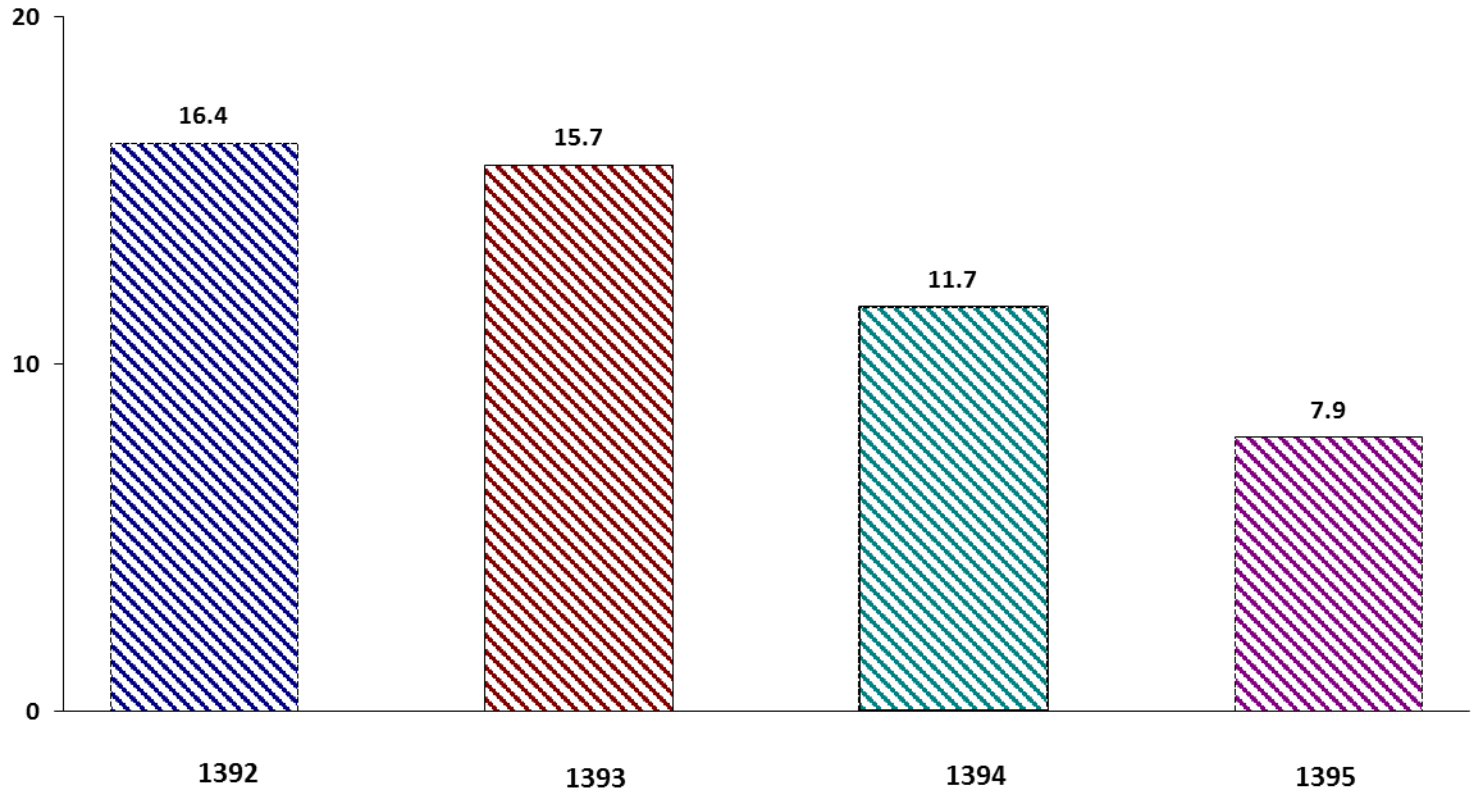
شیوع کلی ناهنجاری های مادرزادی قلبی(در هر ده هزار تولد) در اصفهان(95-1392)



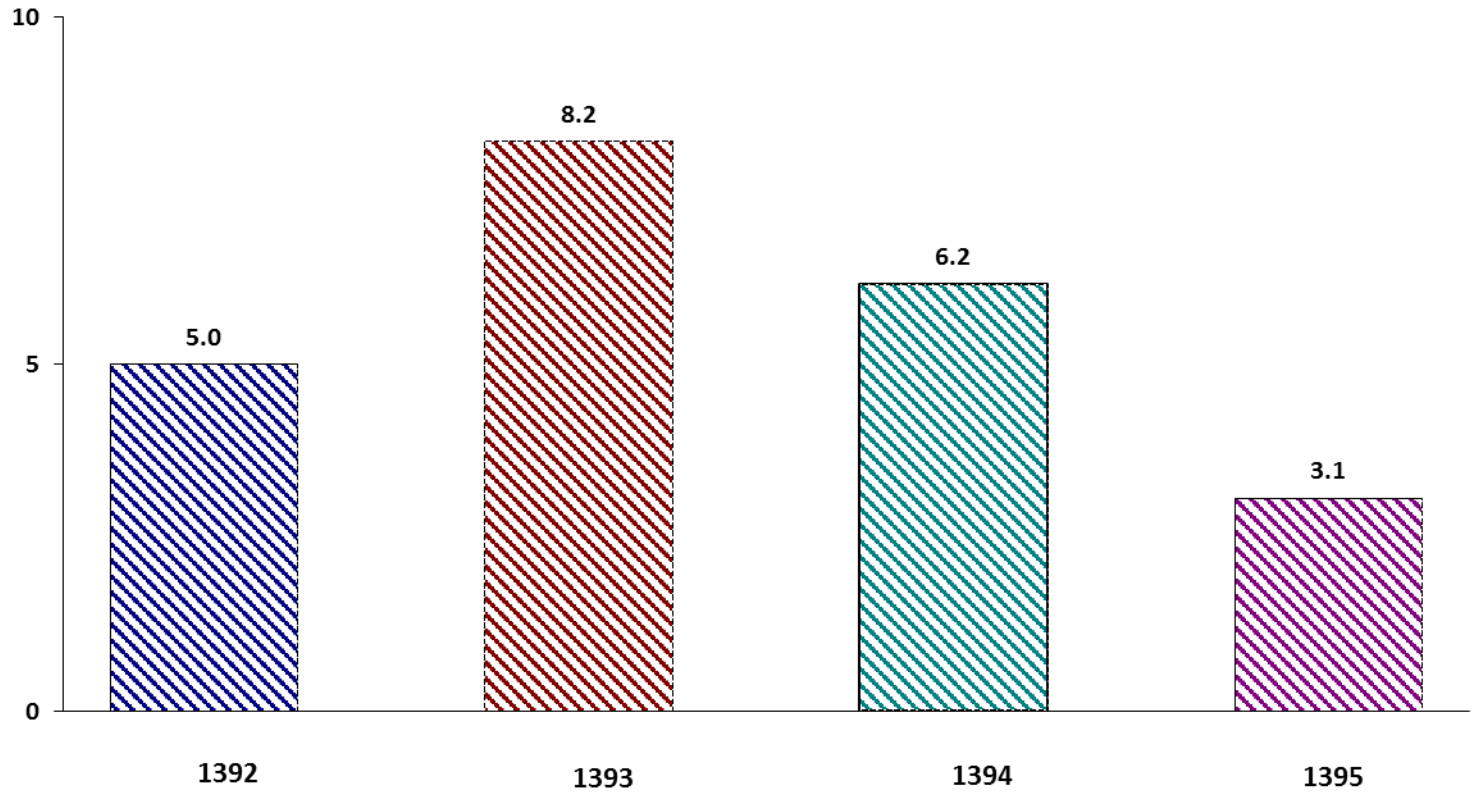
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در اصفهان(95-1392)



شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در اصفهان(95-1392)

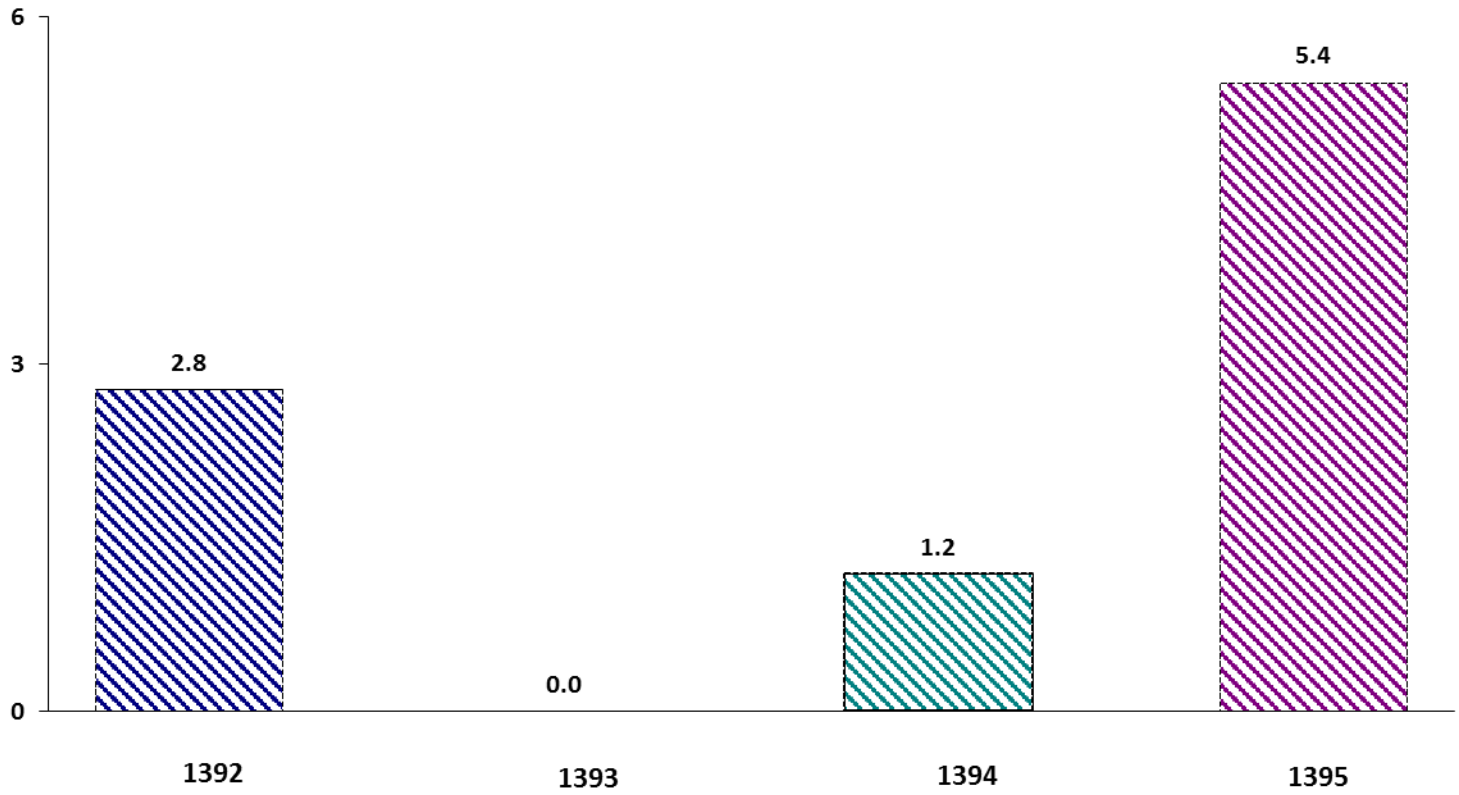


شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در البرز(95-1392)



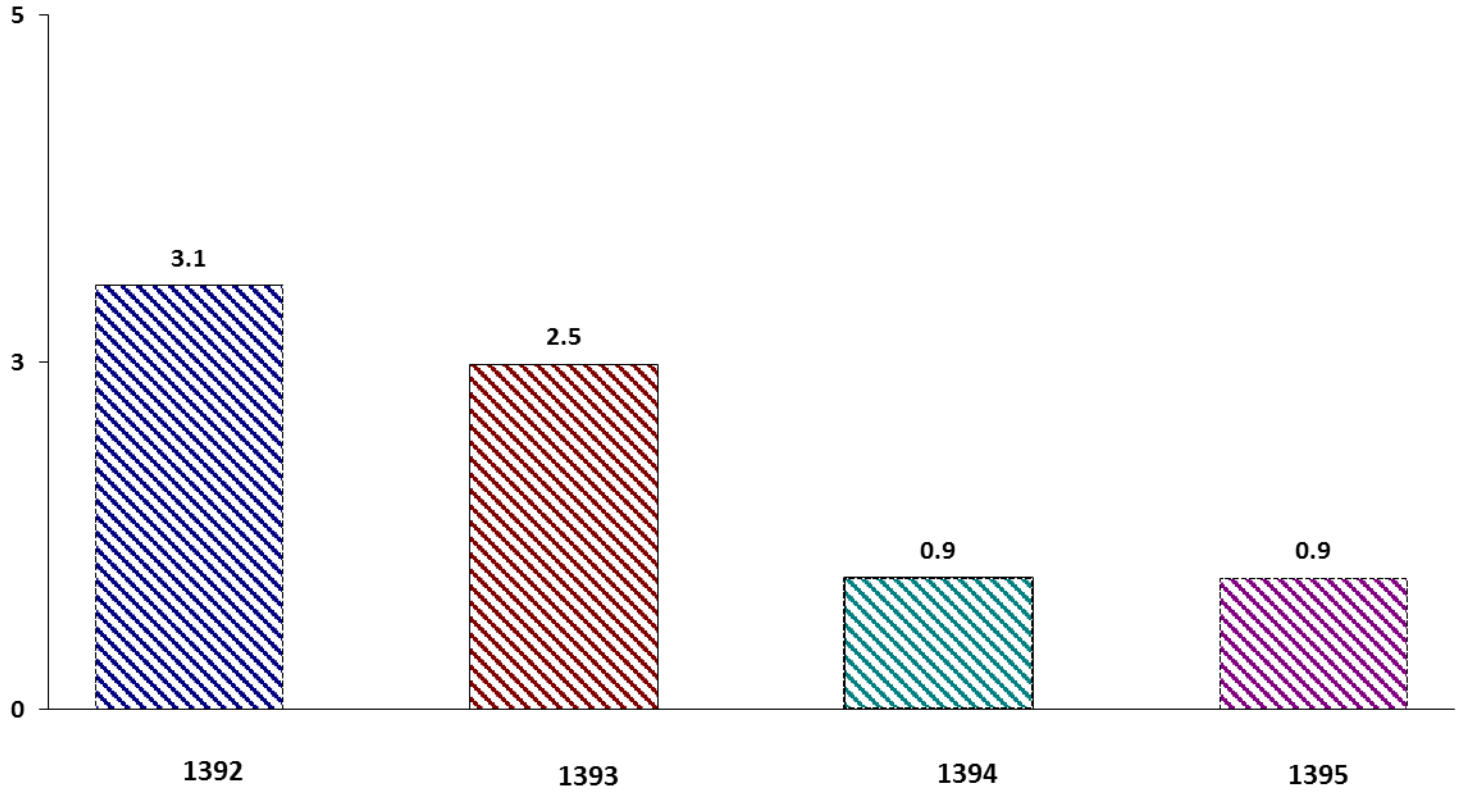
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در البرز(95-1392)

شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در البرز(95-1392)

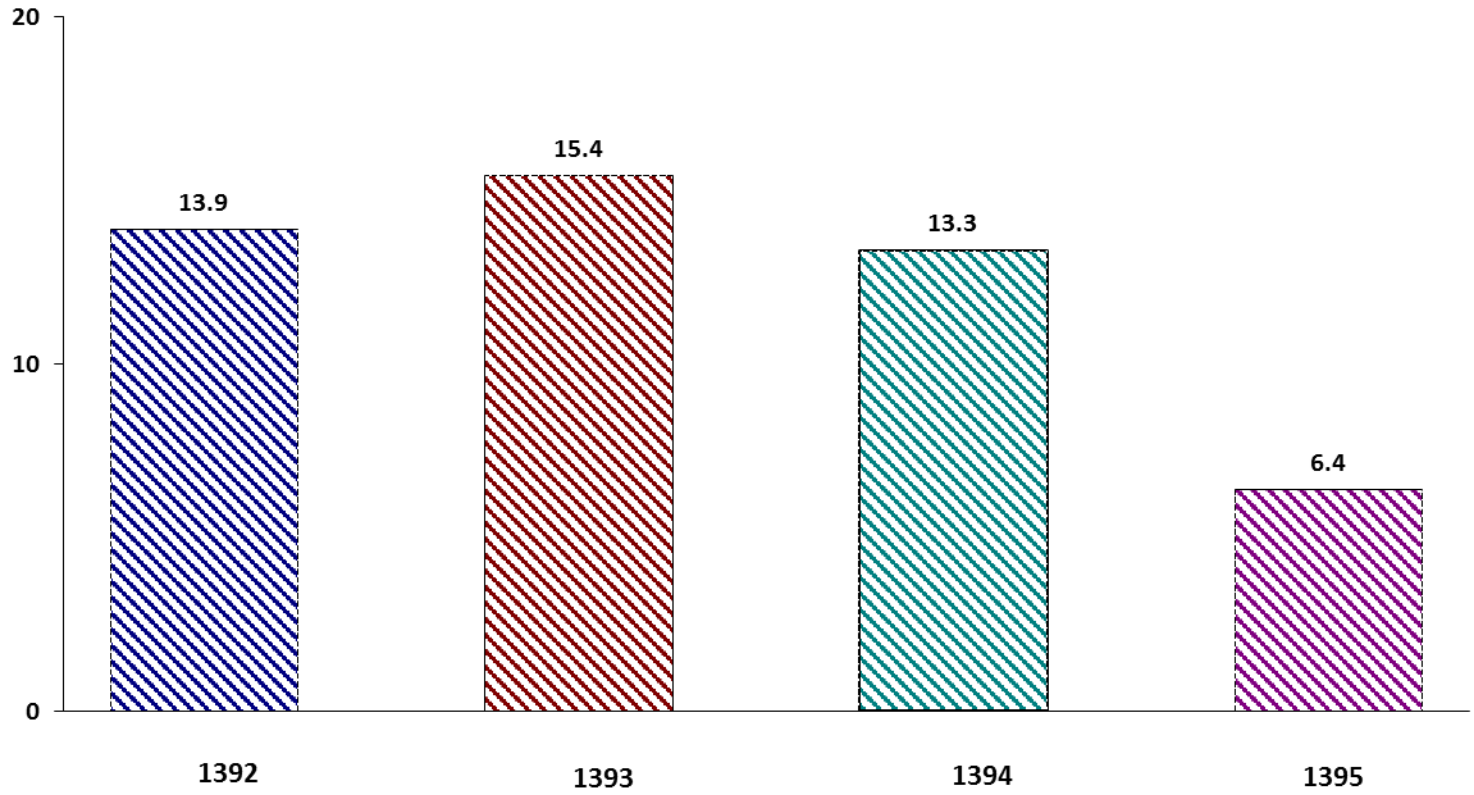


شیوع کلی ناهنجاری های مادرزادی قلبی(در هر ده هزار تولد) در البرز(95-1392)

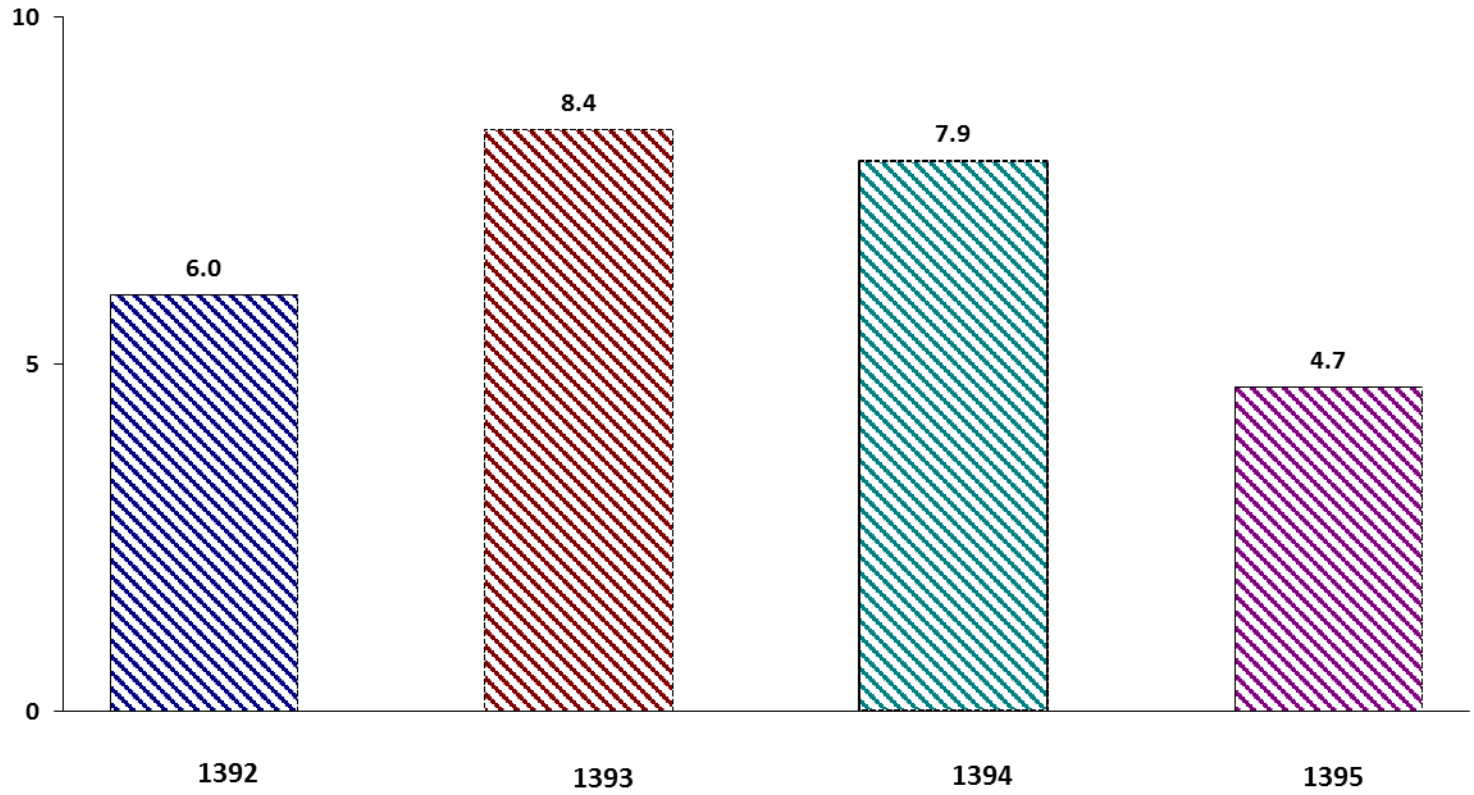
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در البرز(95-1392)



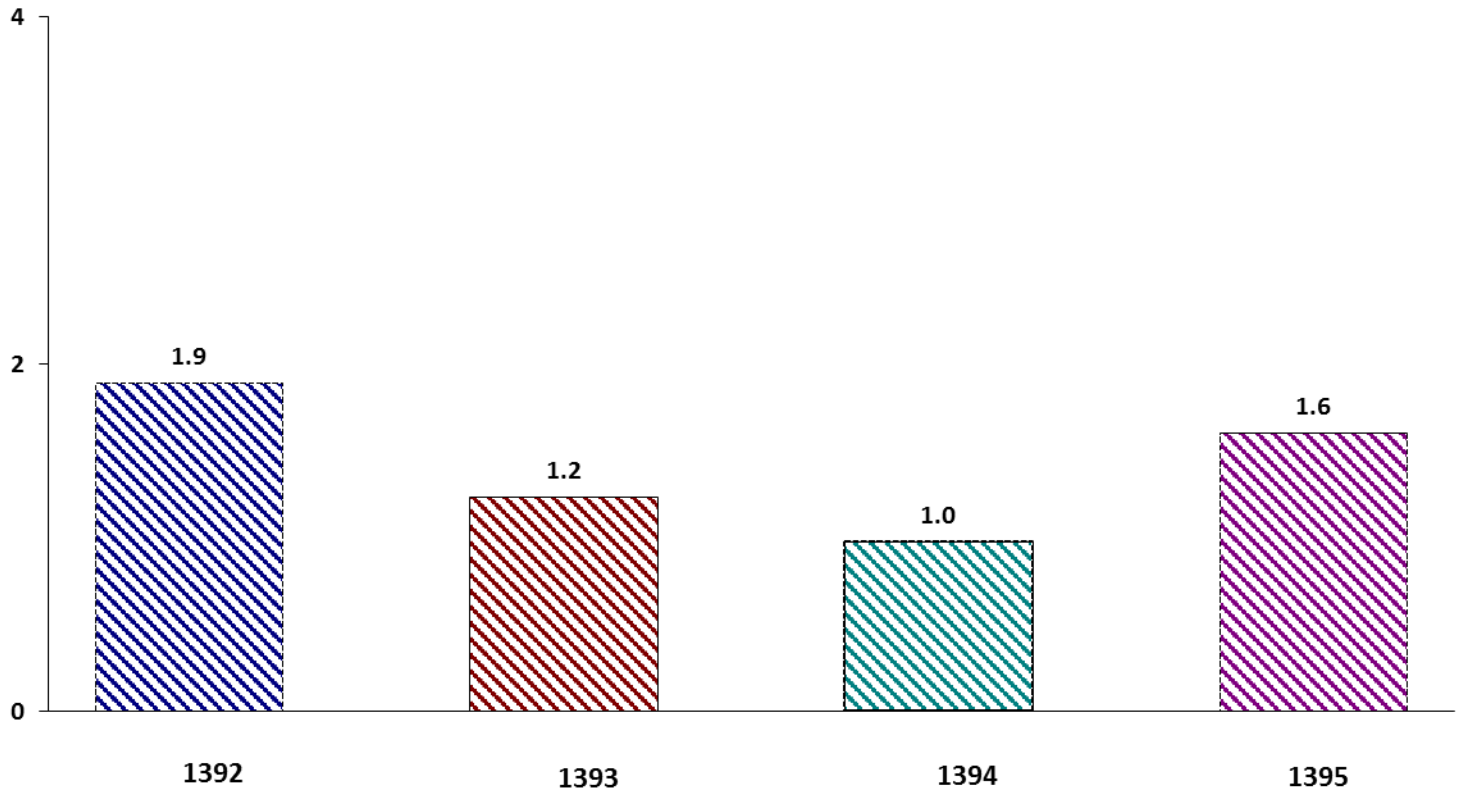
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در البرز(95-1392)



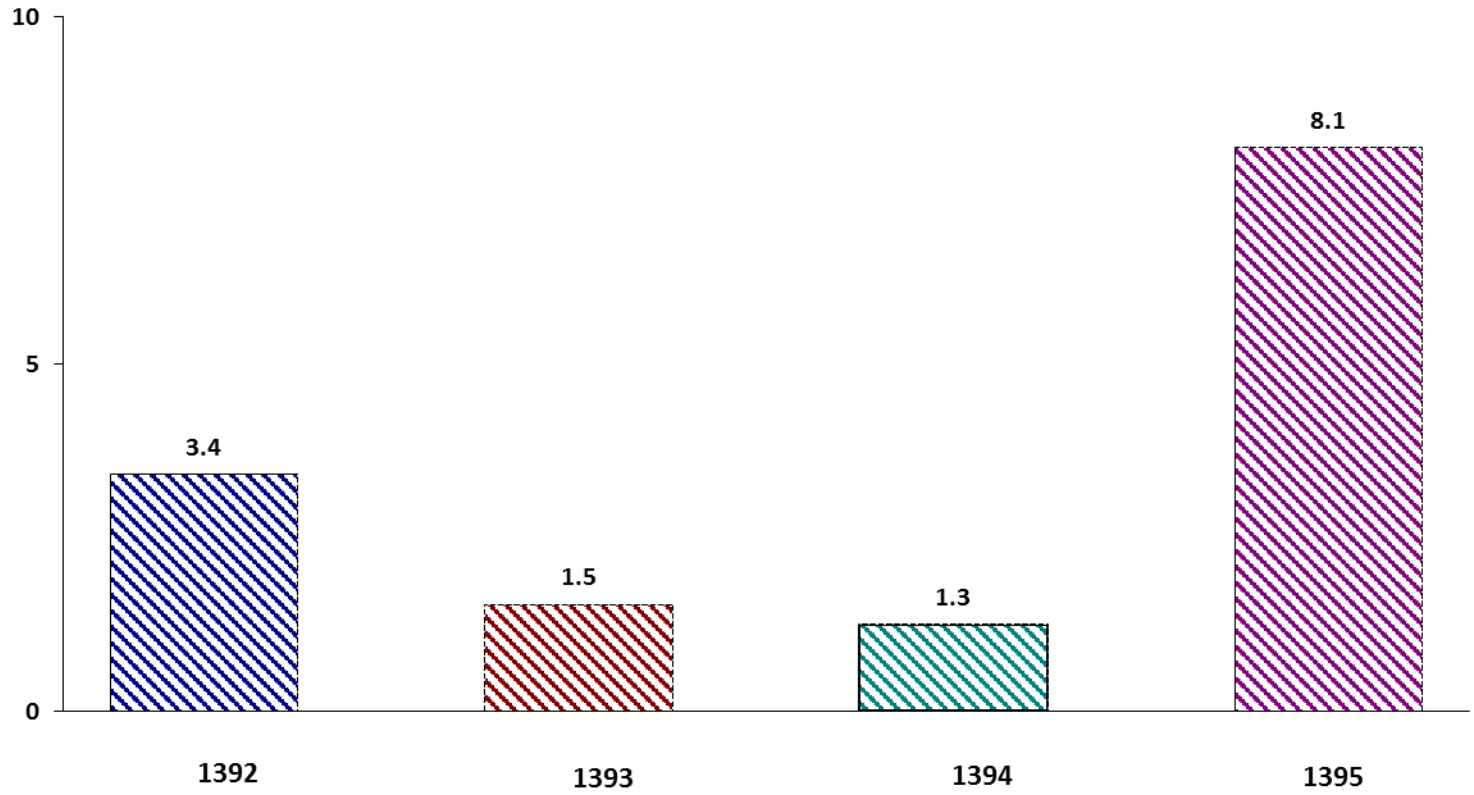
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در ایران(95-1392)



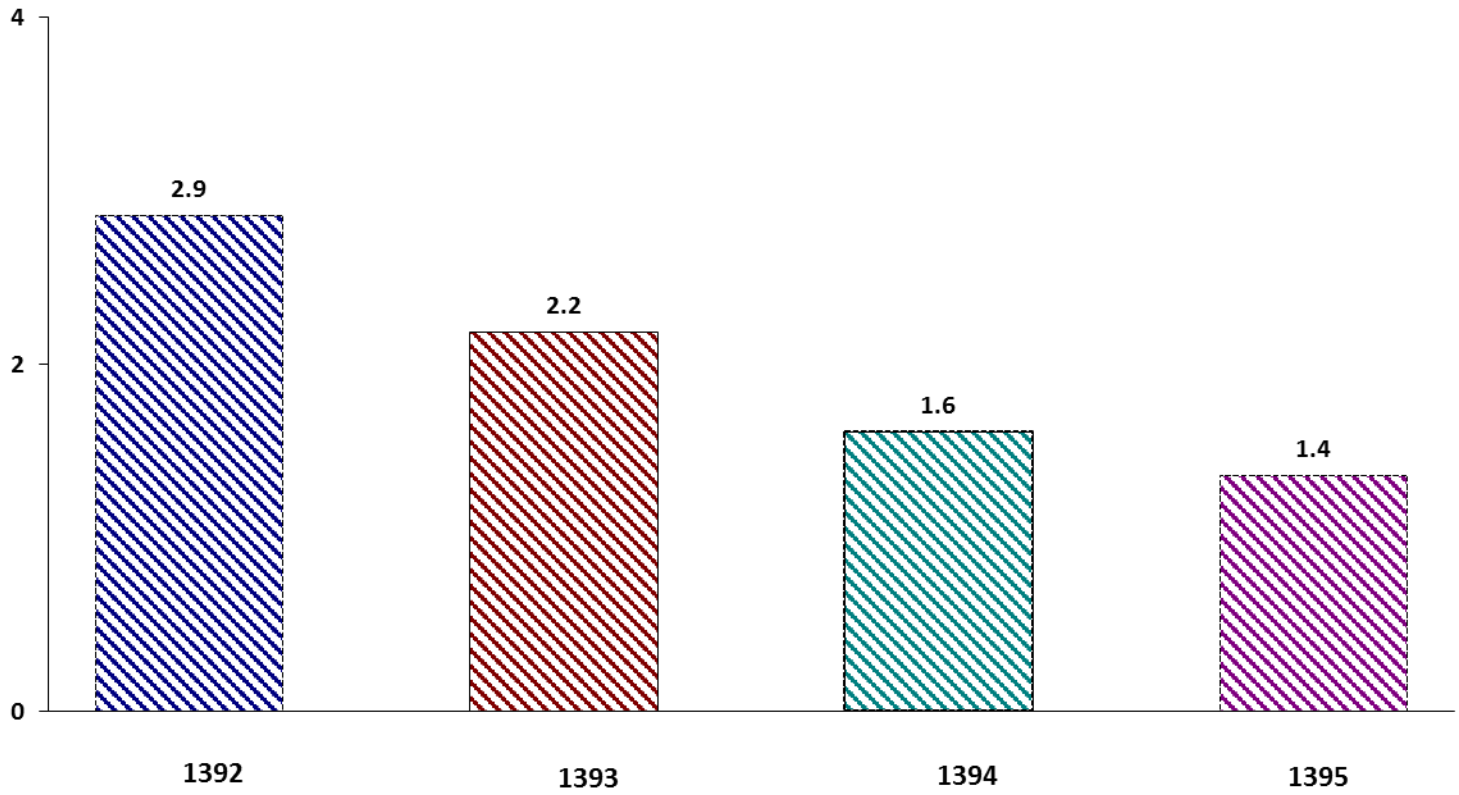
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در ایران(95-1392)



شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در ایران(95-1392)

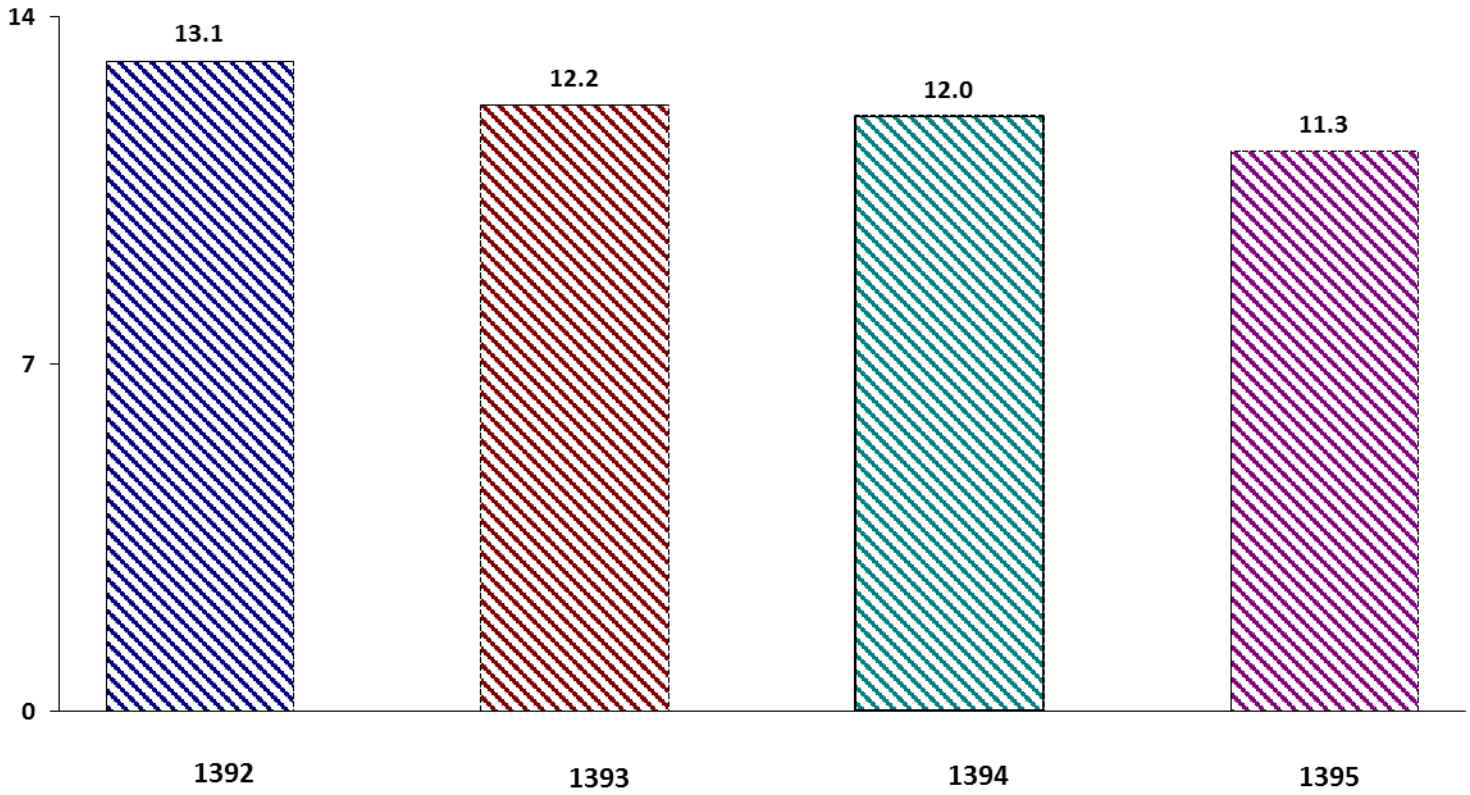


شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در ایران(95-1392)

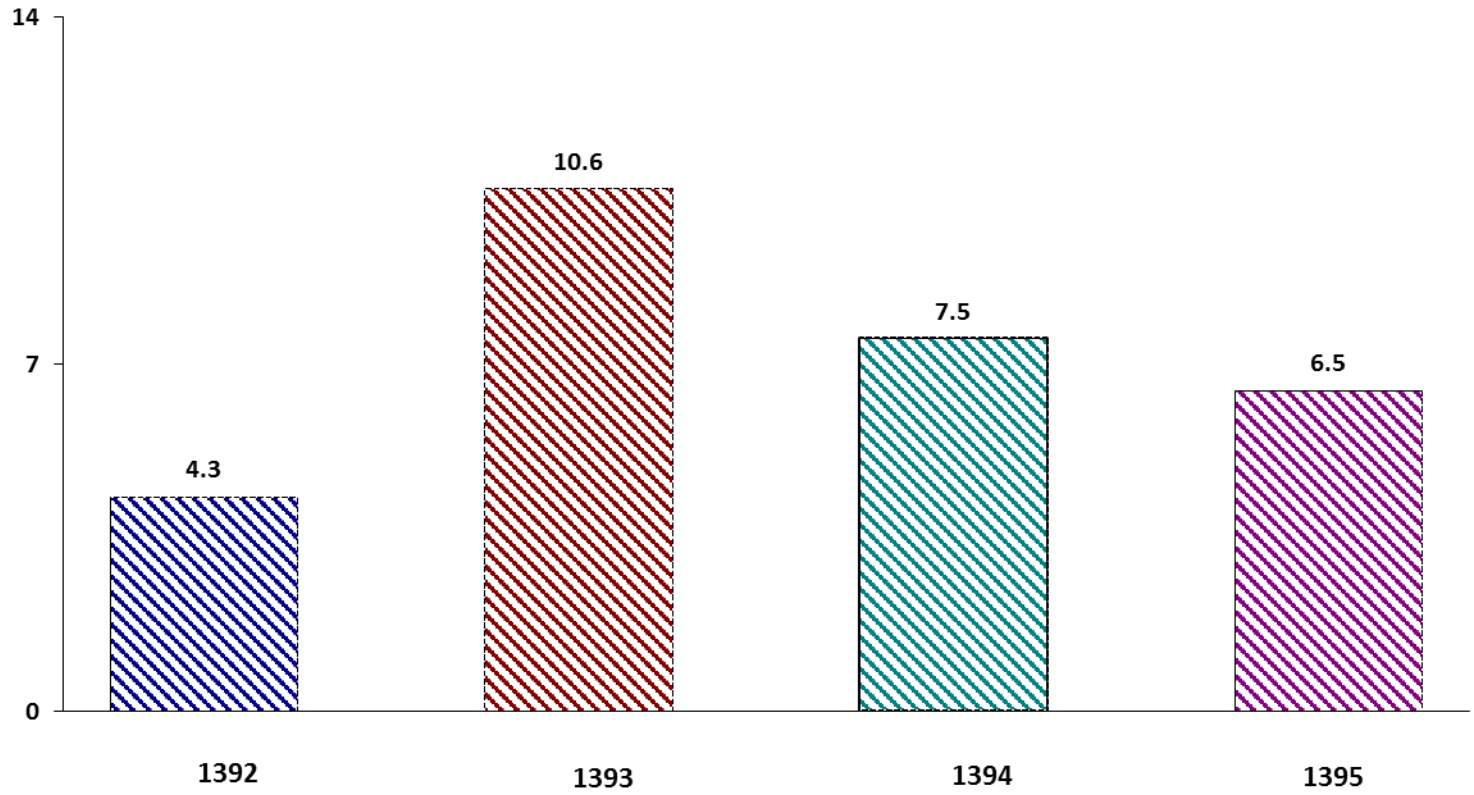


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در ایران(95-1392)

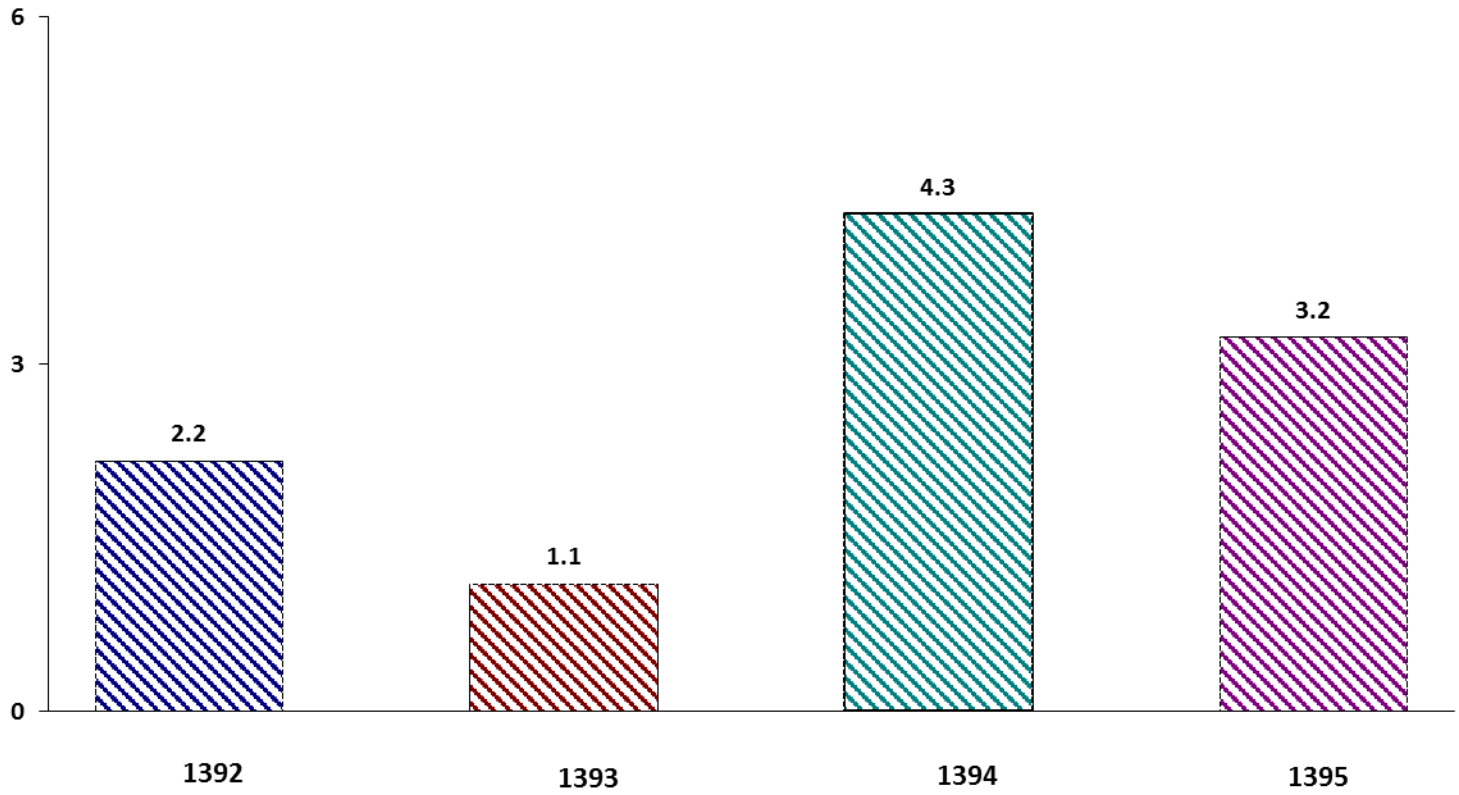
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در ایران(95-1392)



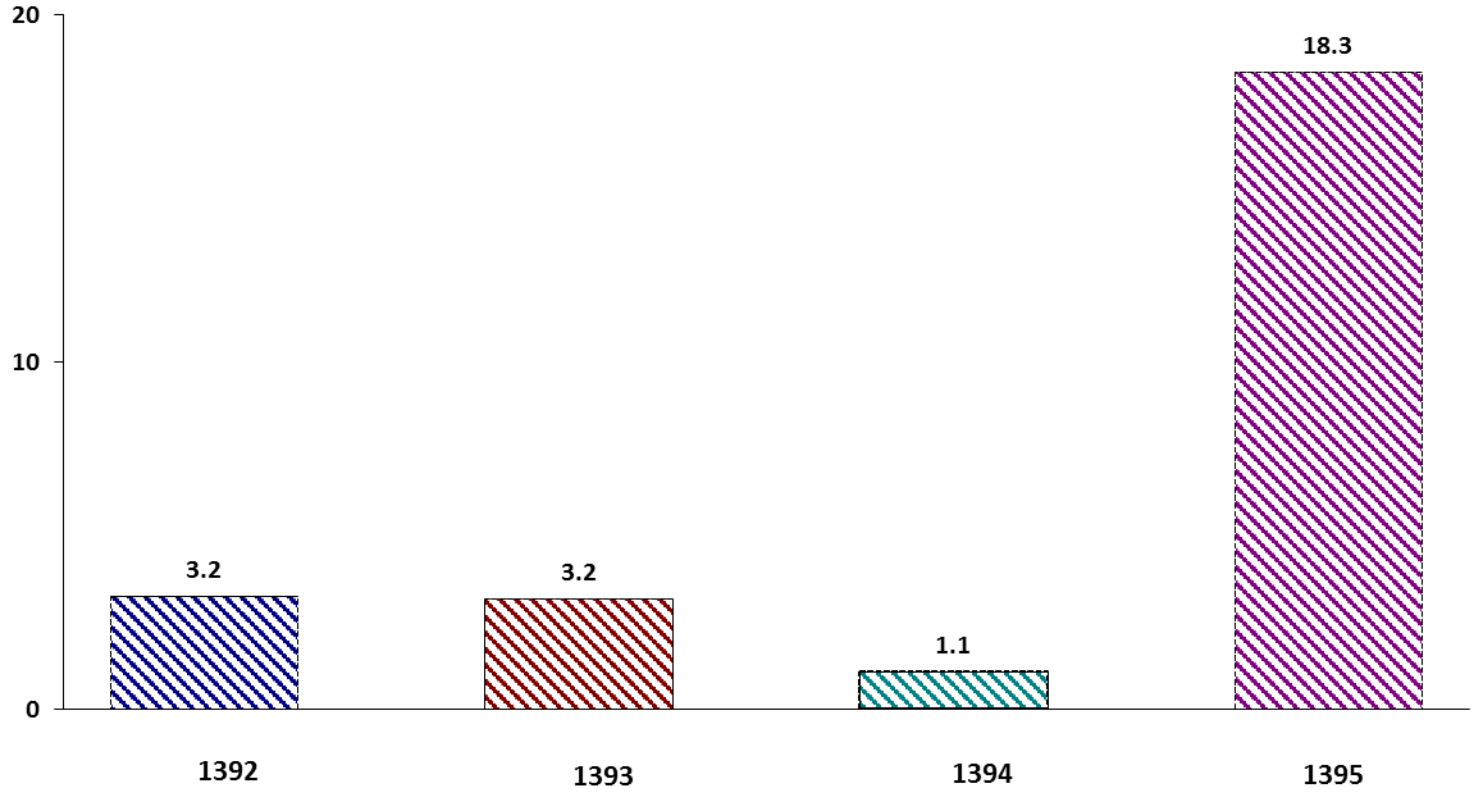
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در ایلام(95-1392)



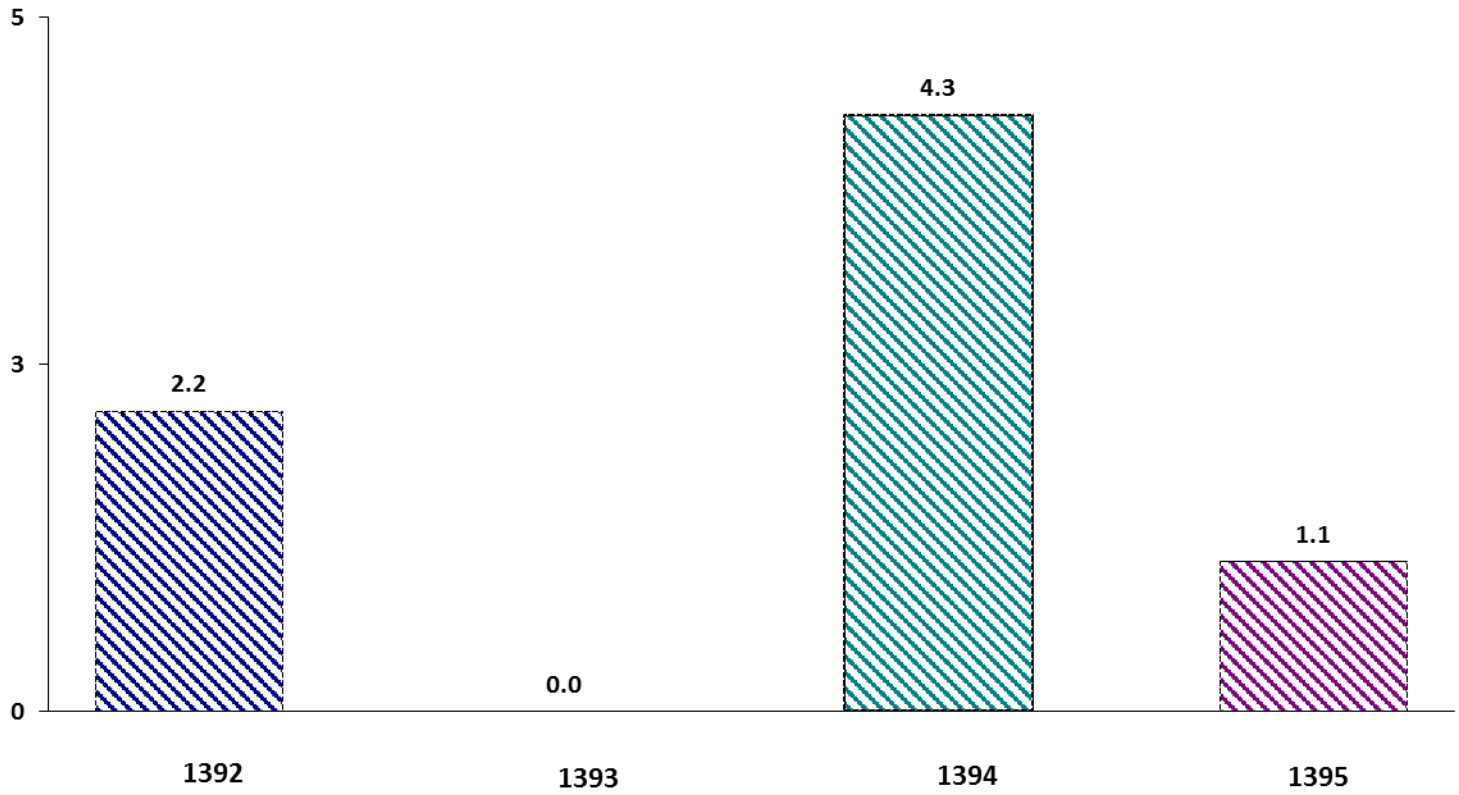
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در ایلام(95-1392)



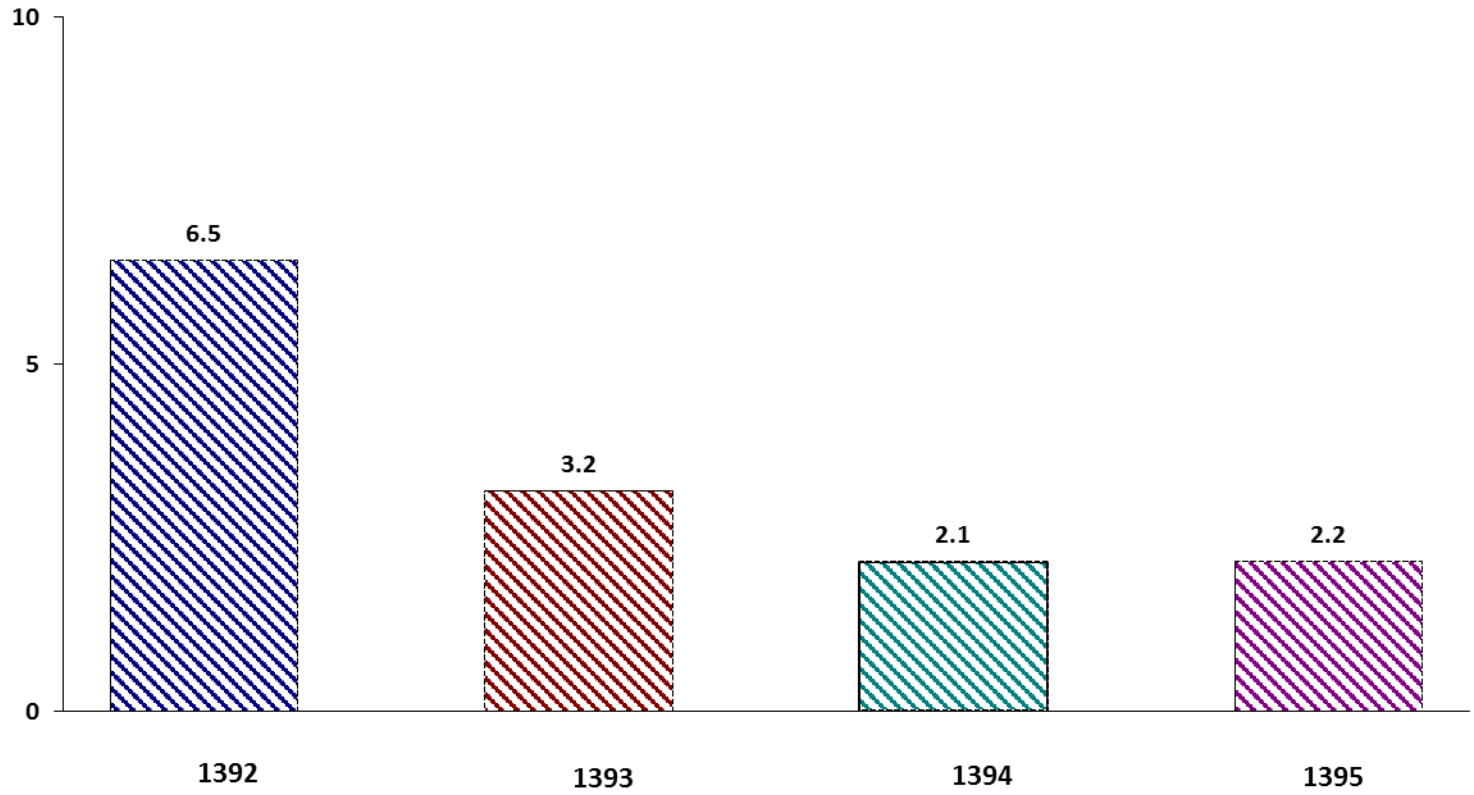
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در ایلام(95-1392)



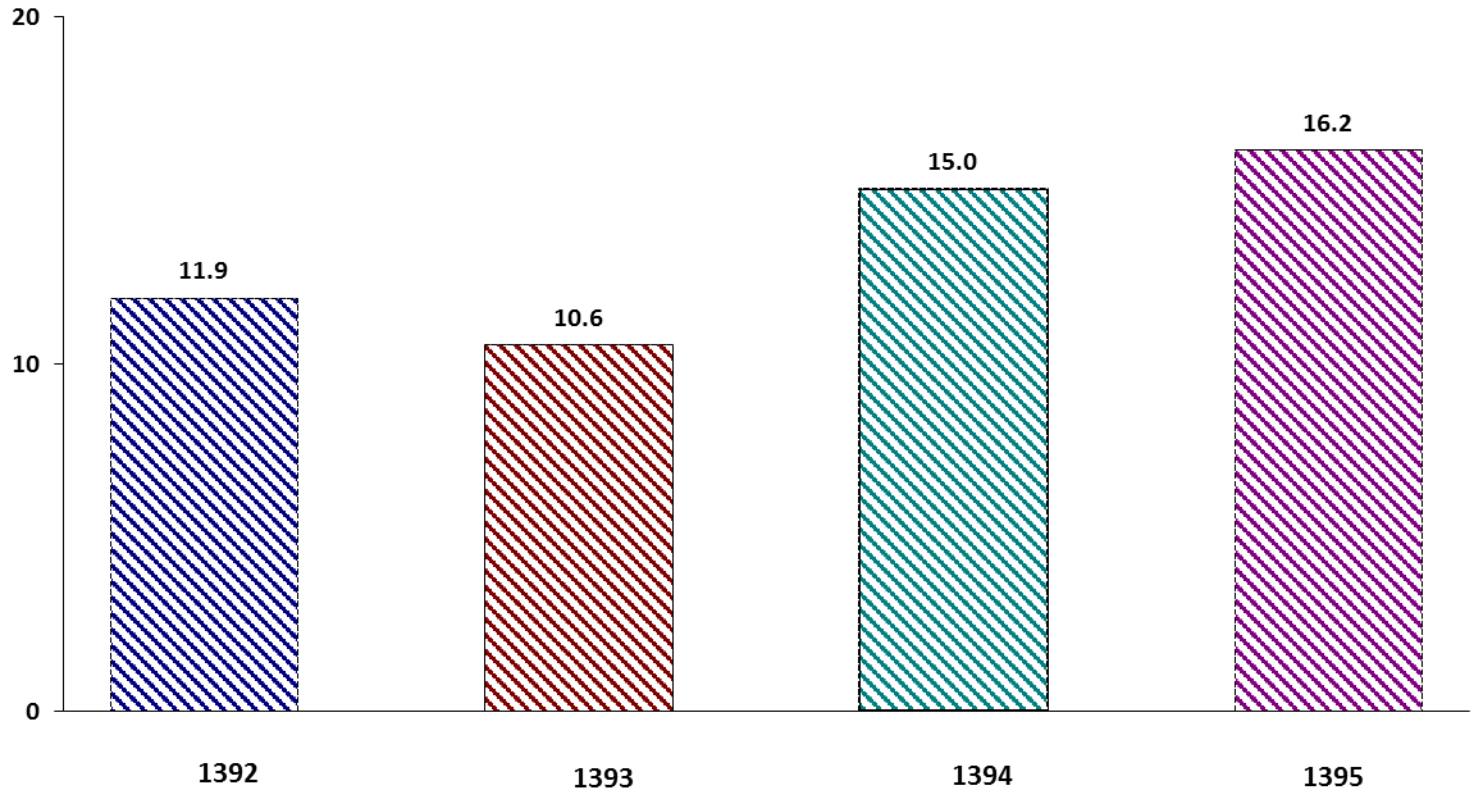
شیوع کلی ناهنجاری های مادرزادی قلبی(در هر ده هزار تولد) در ایلام(95-1392)



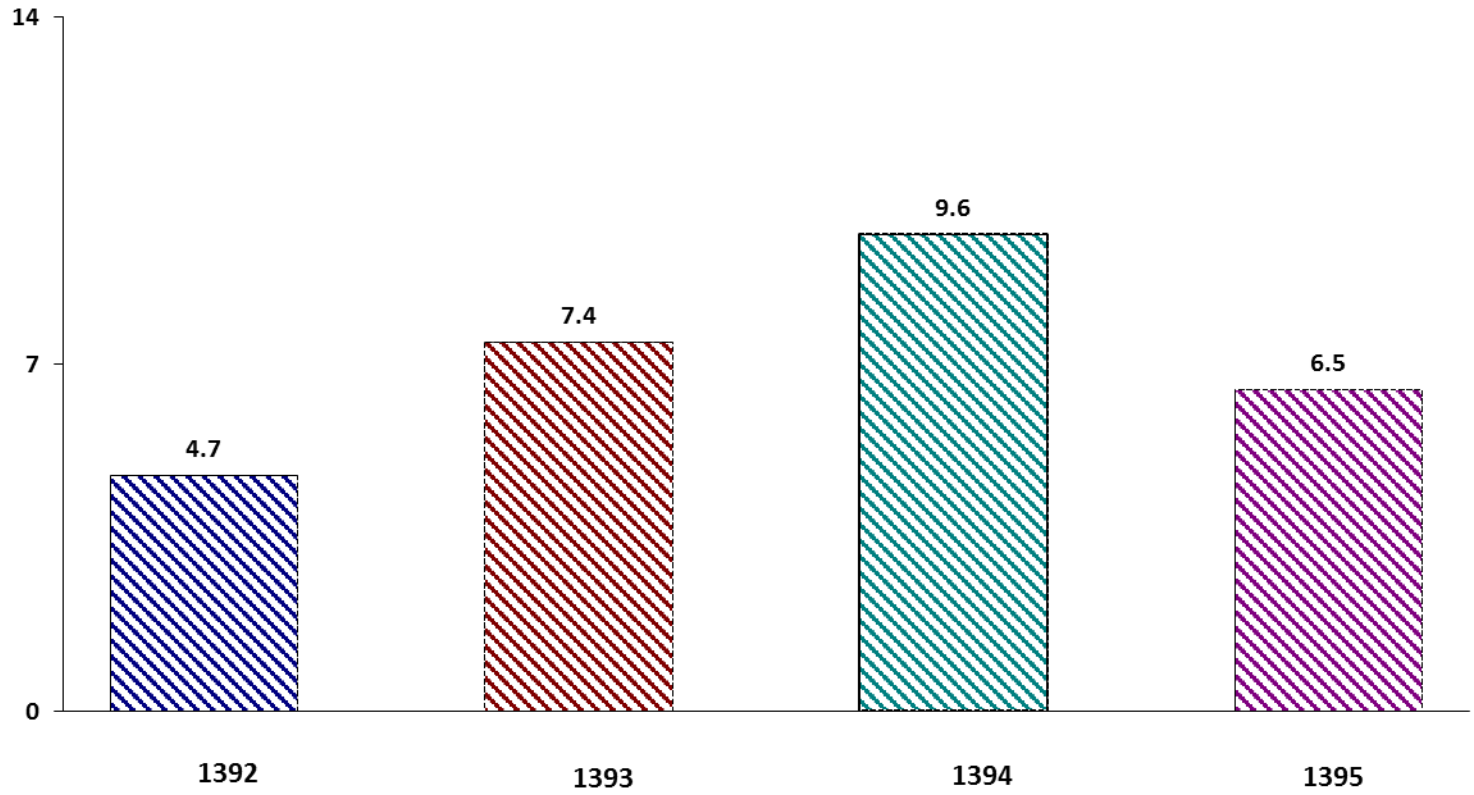
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در ایلام(95-1392)



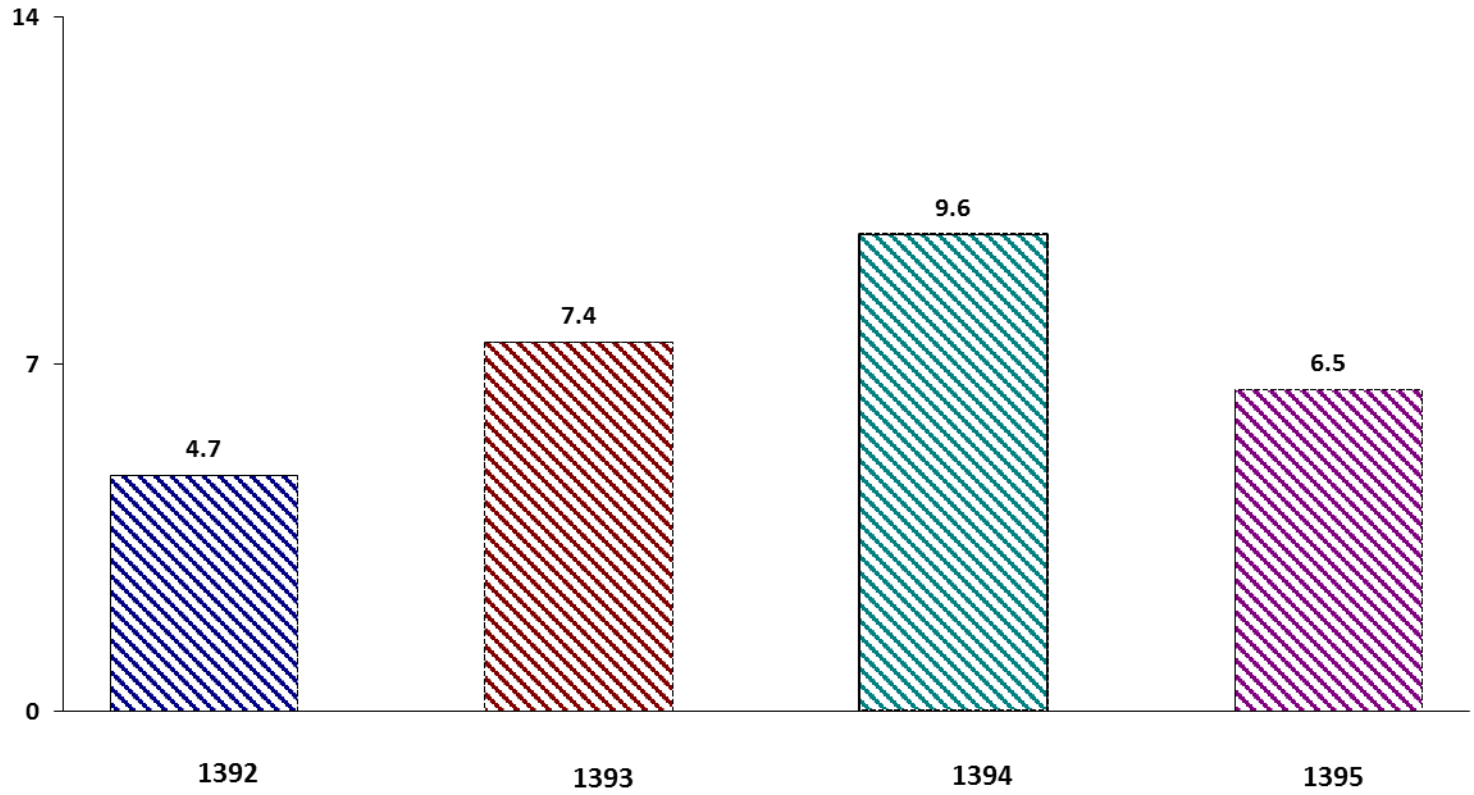
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در ایلام(95-1392)



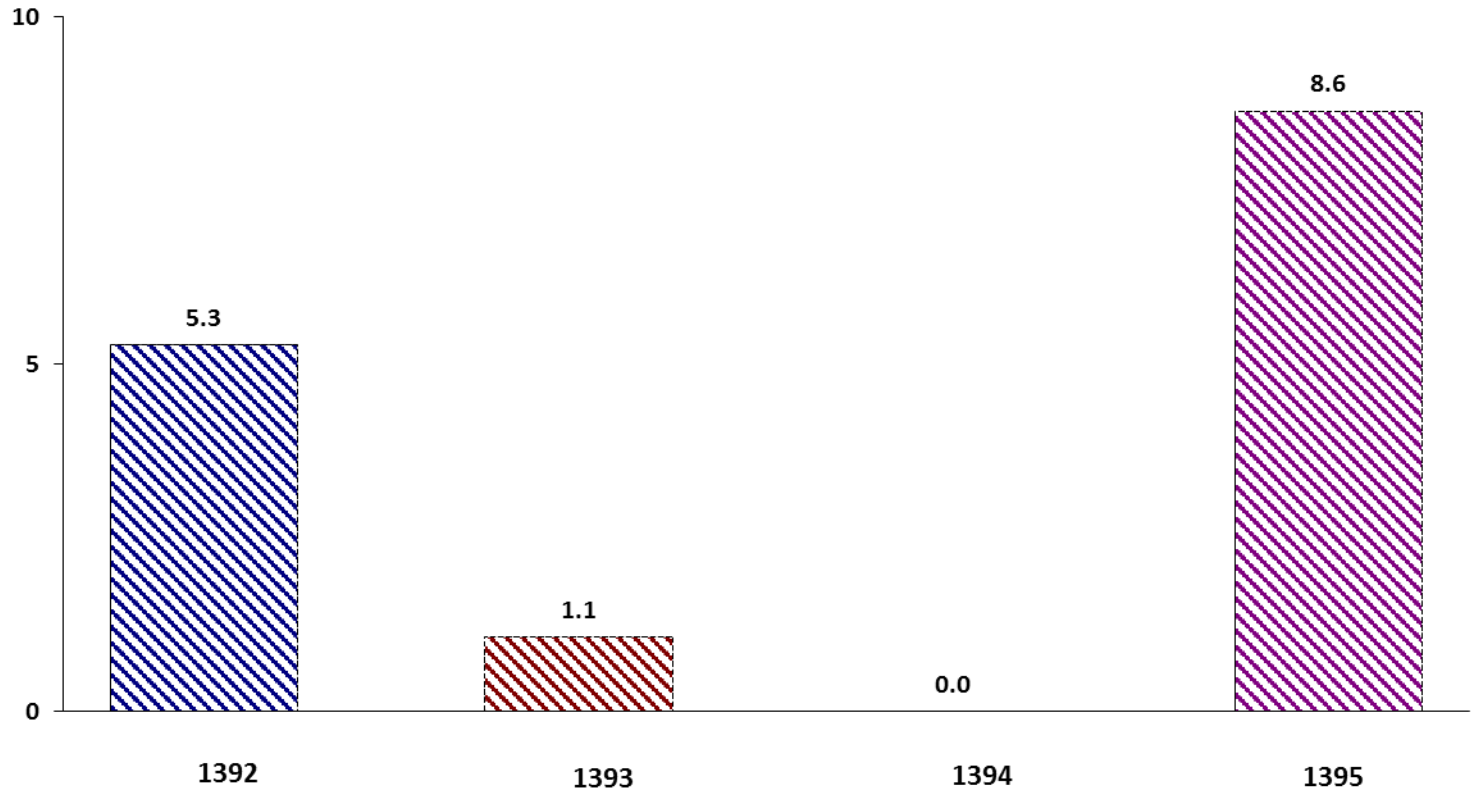
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در بوشهر(95-1392)



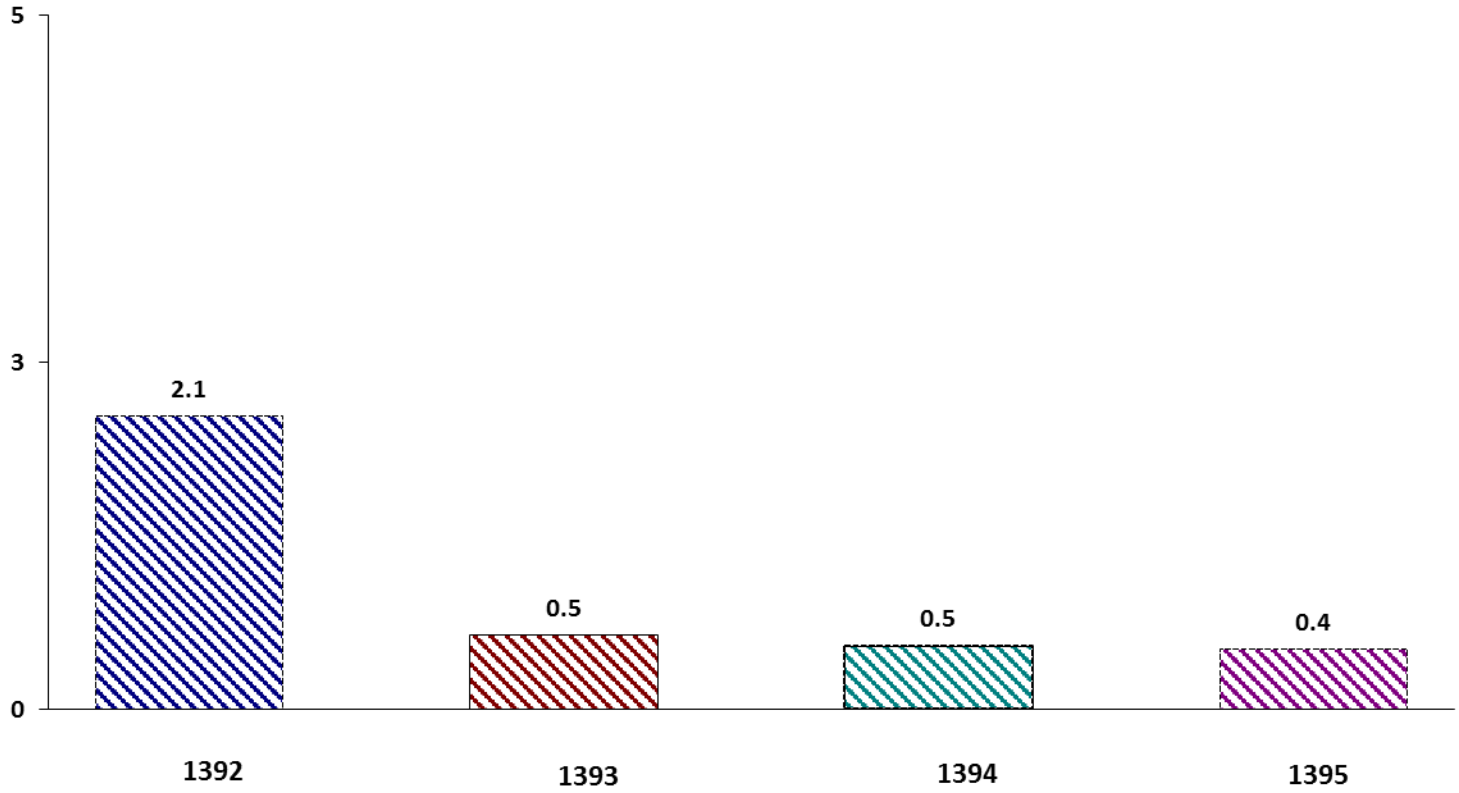
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در بوشهر(95-1392)



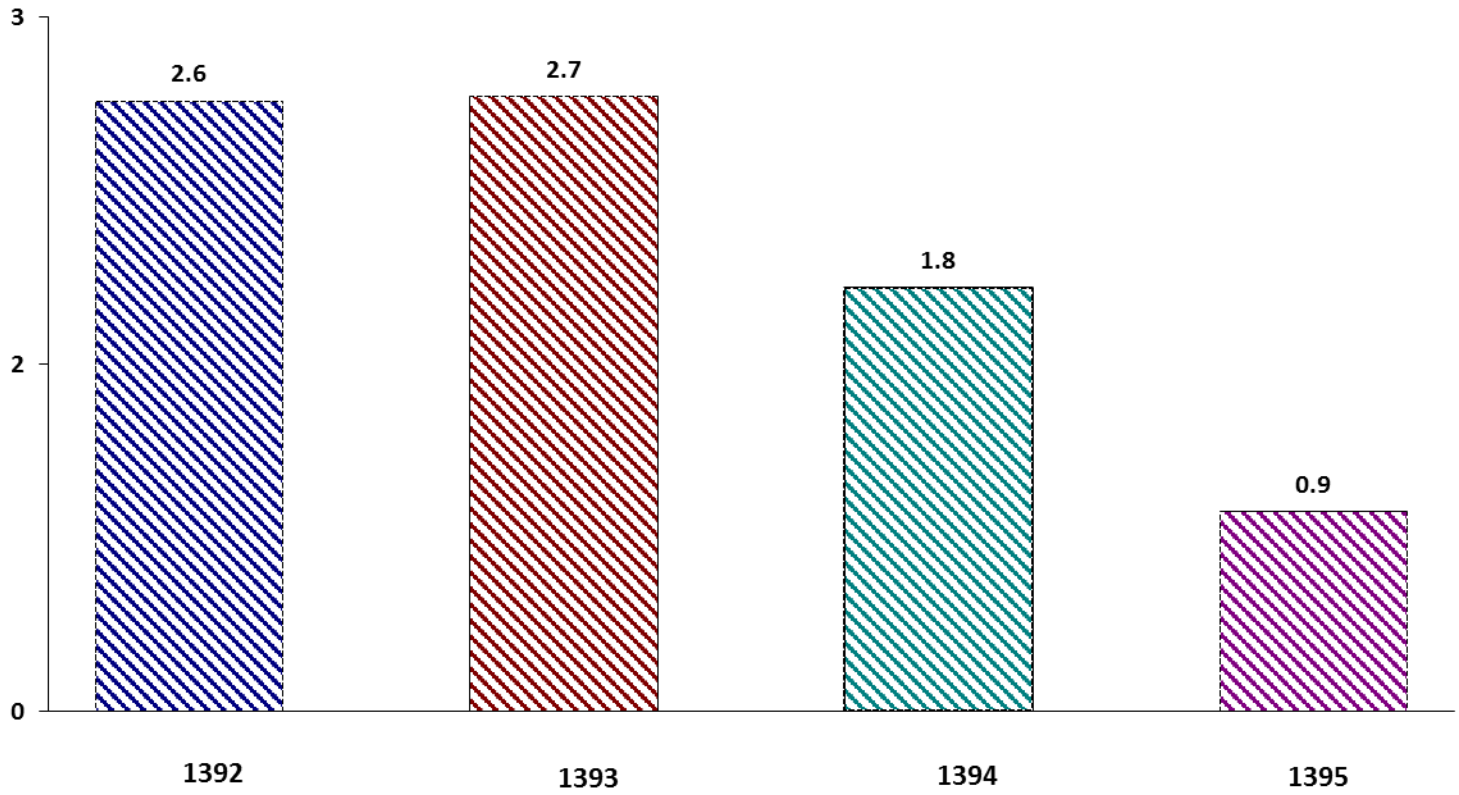
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در بوشهر(95-1392)



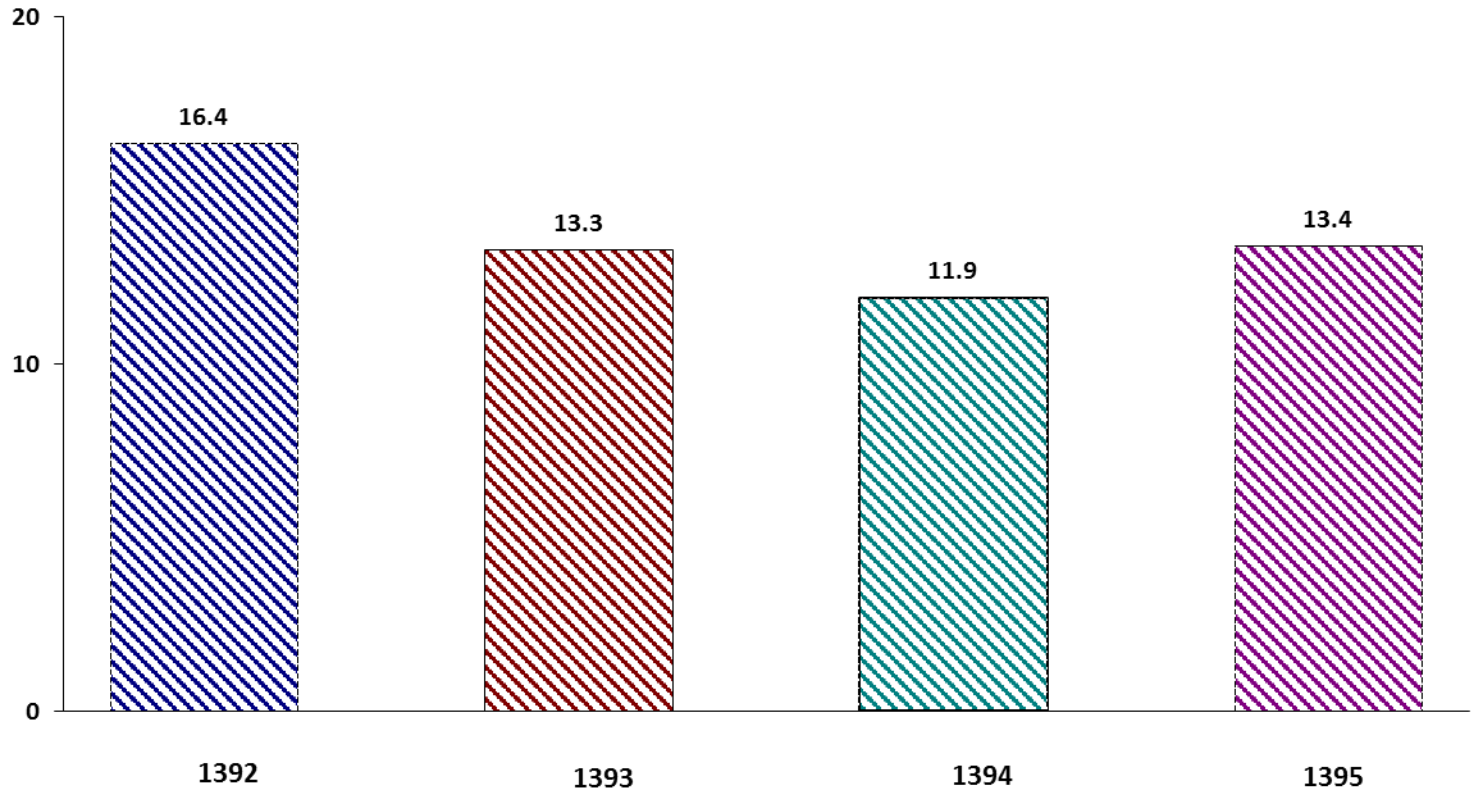
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در بوشهر(95-1392)



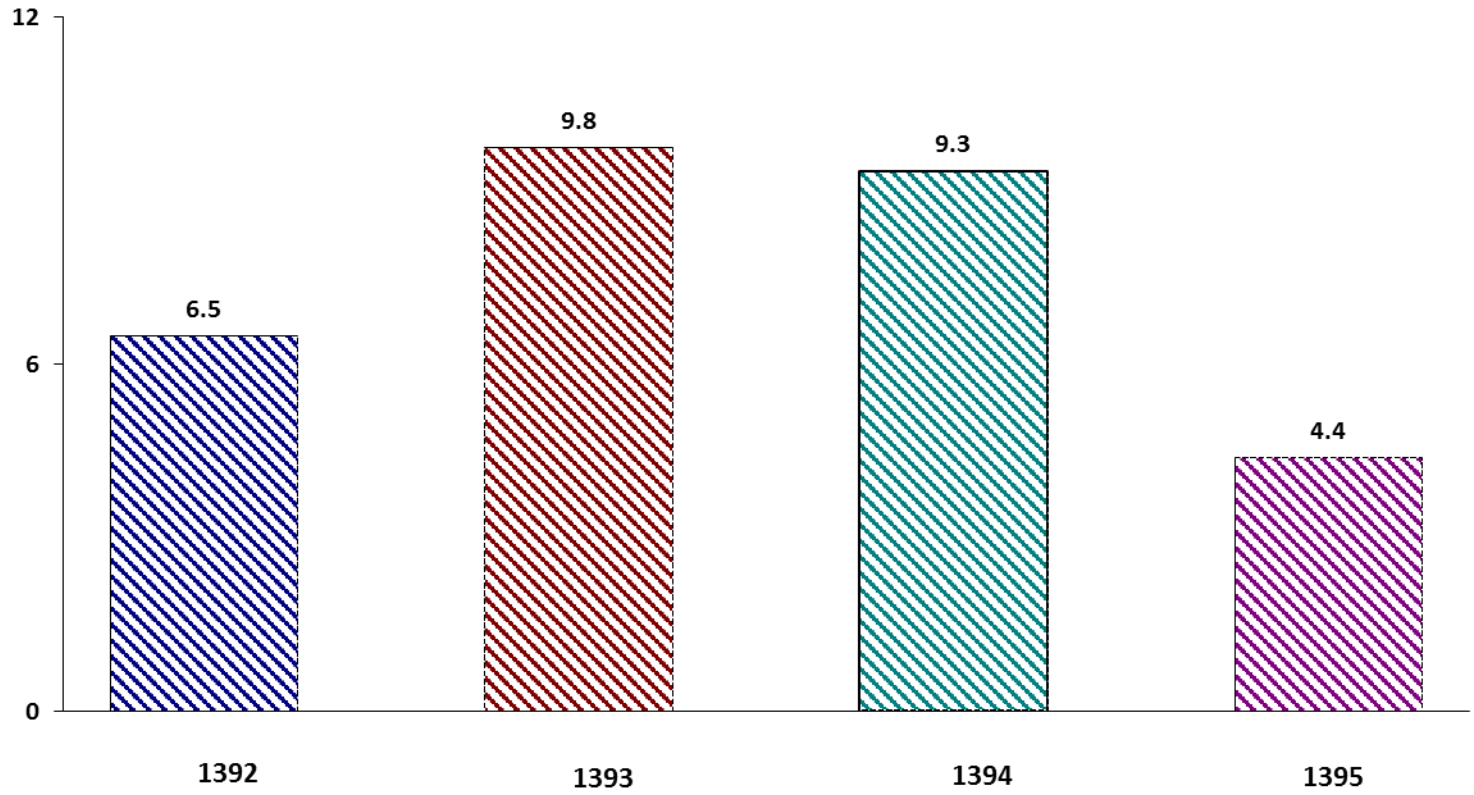
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در بوشهر(95-1392)



شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در بوشهر(95-1392)

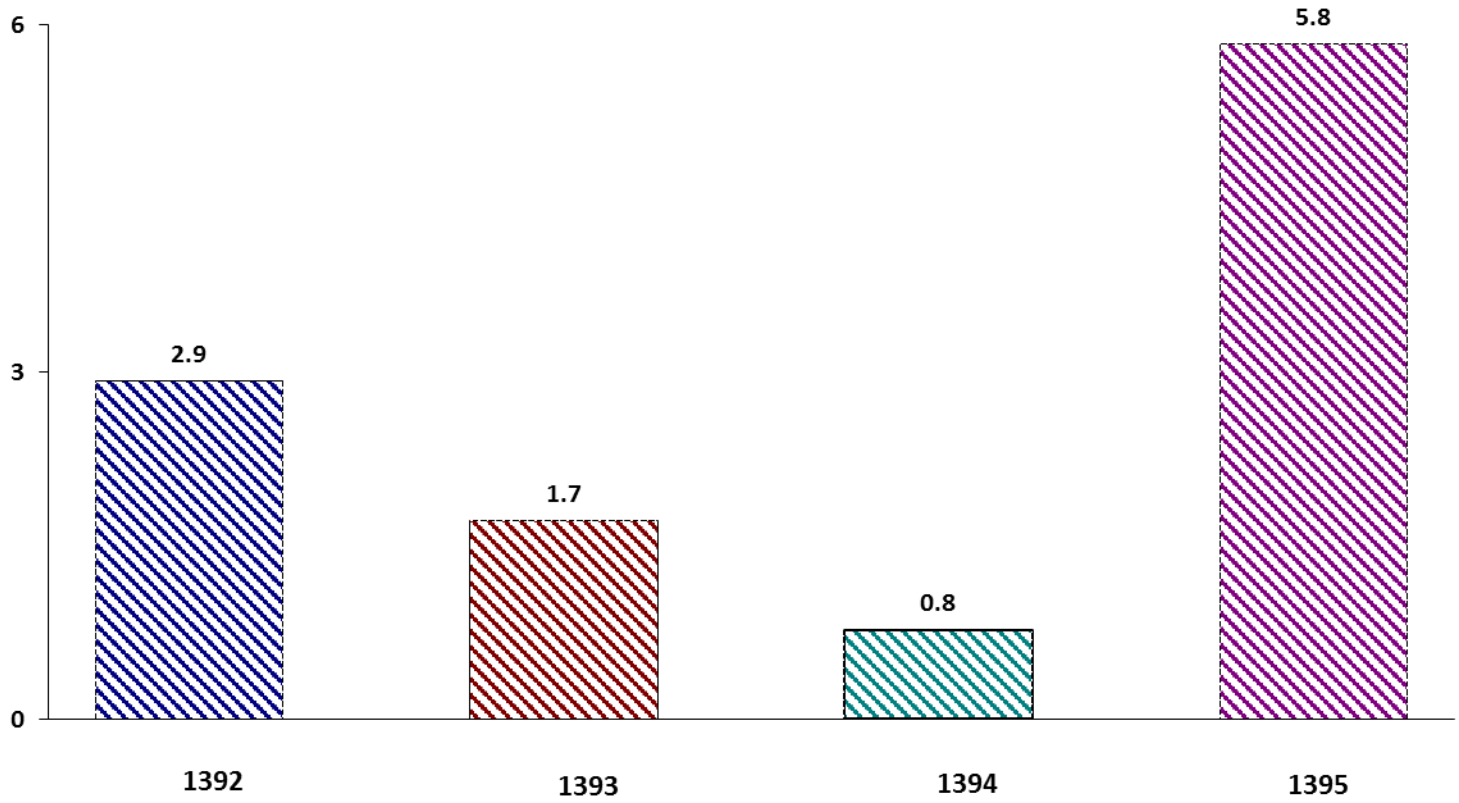


شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در تهران(95-1392)

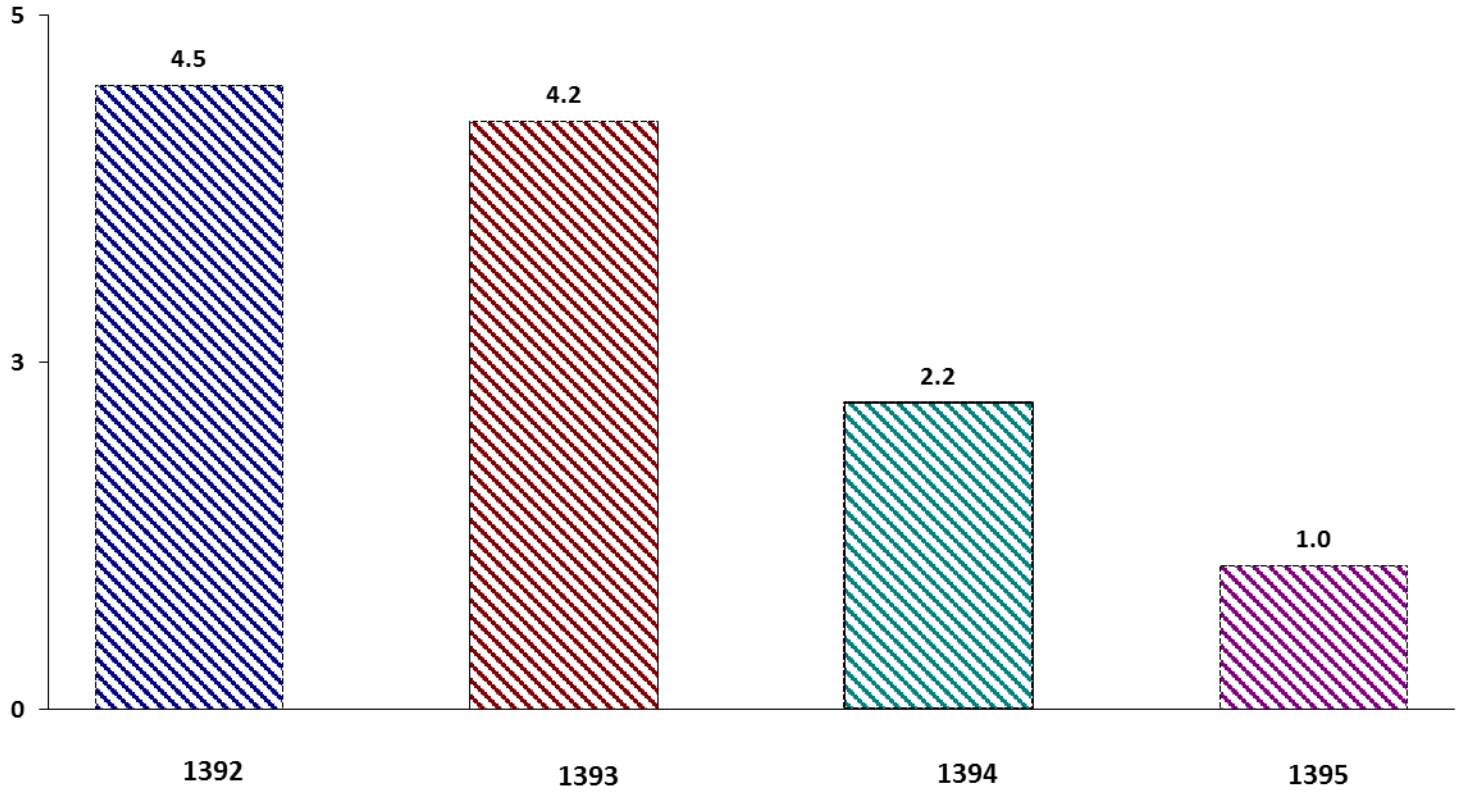


شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در تهران(95-1392)

شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در تهران(95-1392)

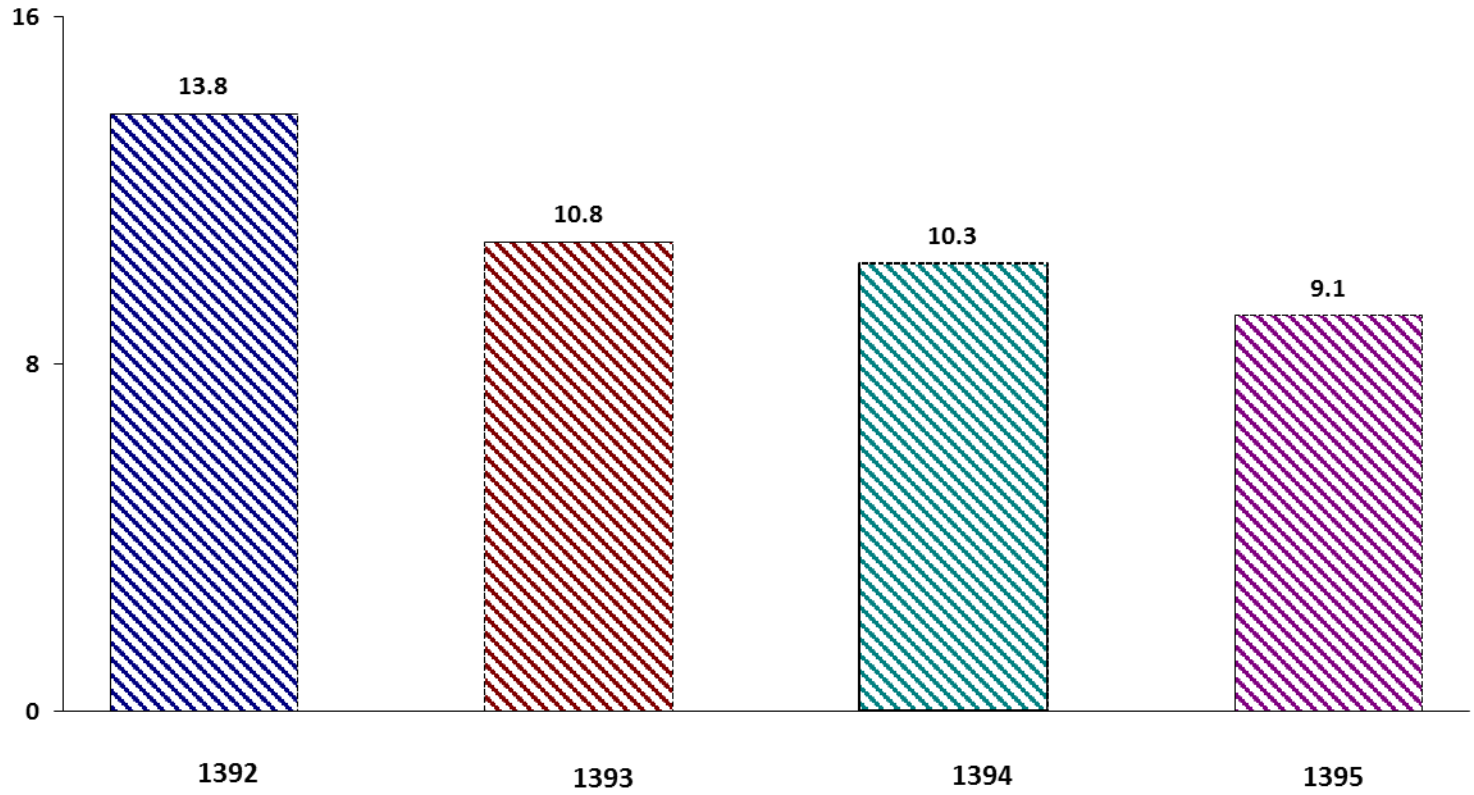


شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در تهران(95-1392)

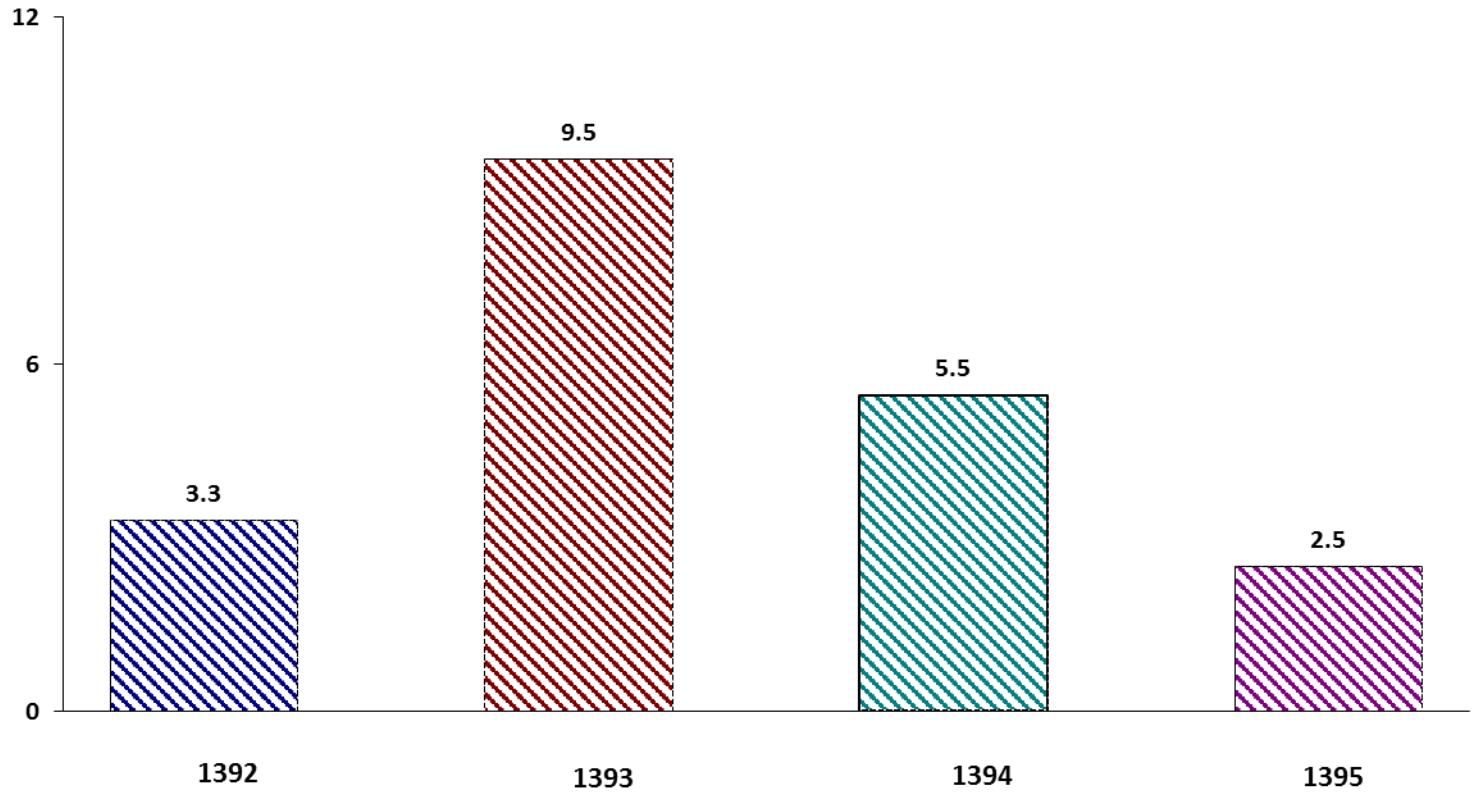


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در تهران(95-1392)

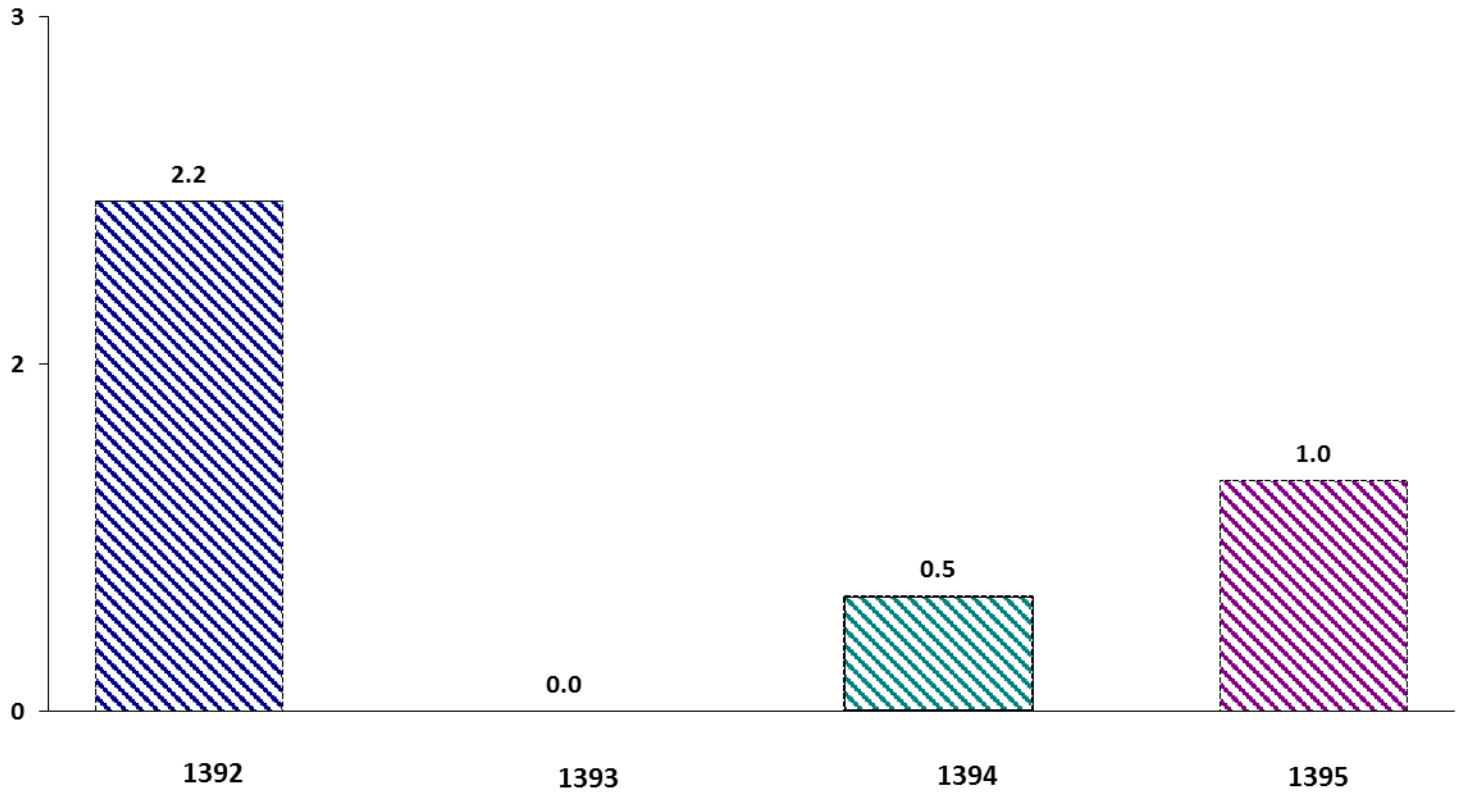
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در تهران(95-1392)



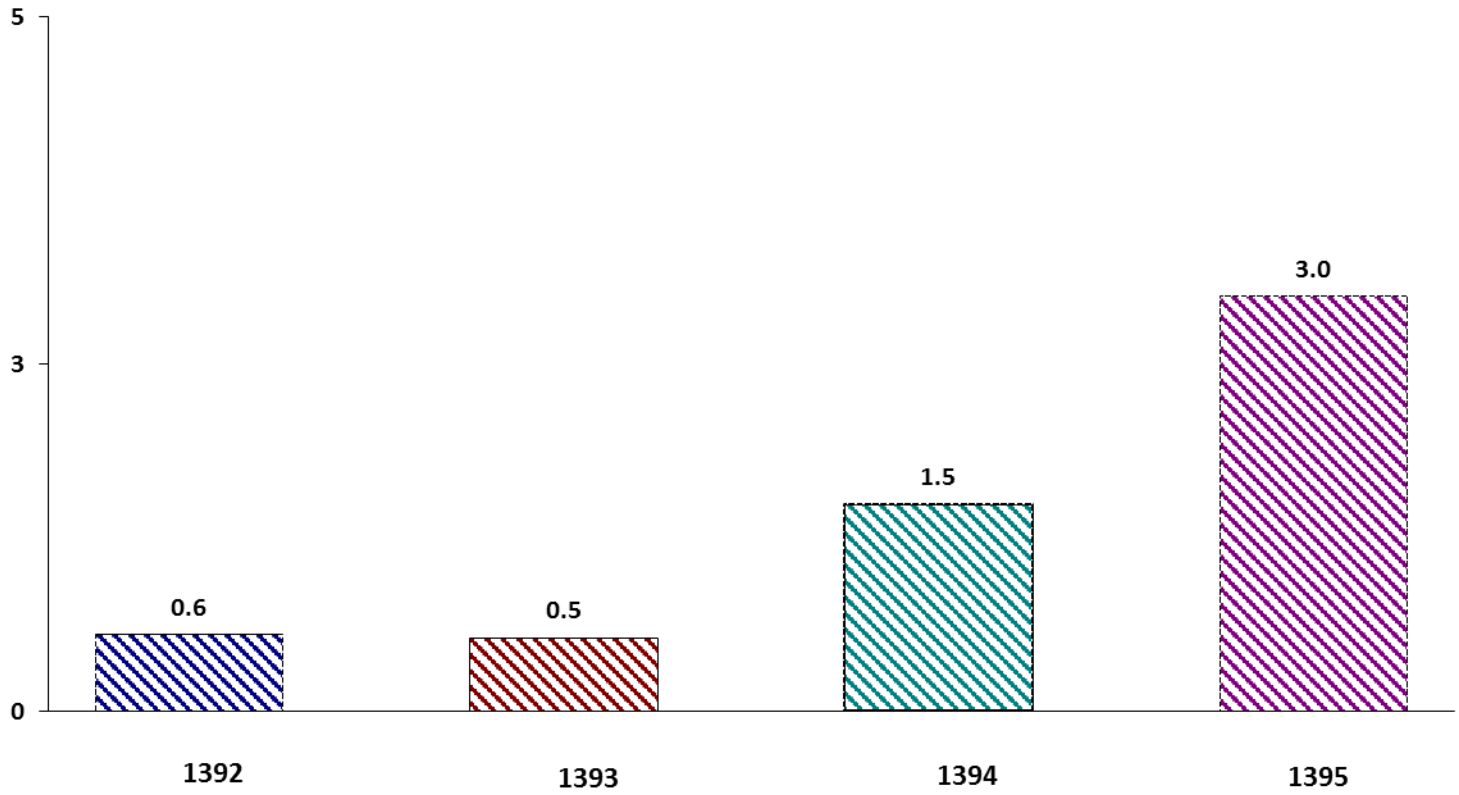
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري (در هر ده هزار تولد) در چهار محال بختياري(95-1392)



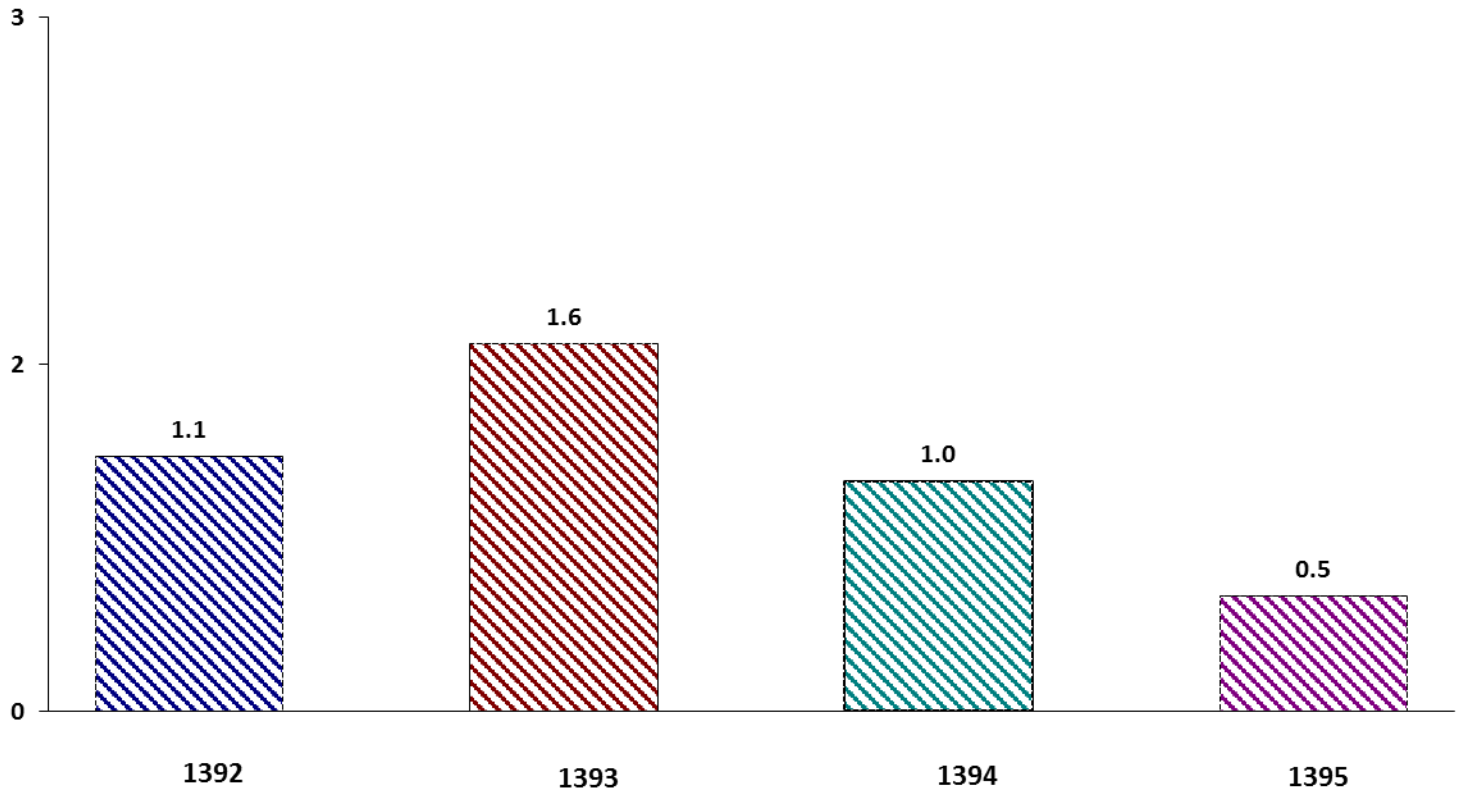
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در چهار محال بختیاري(95-1392)



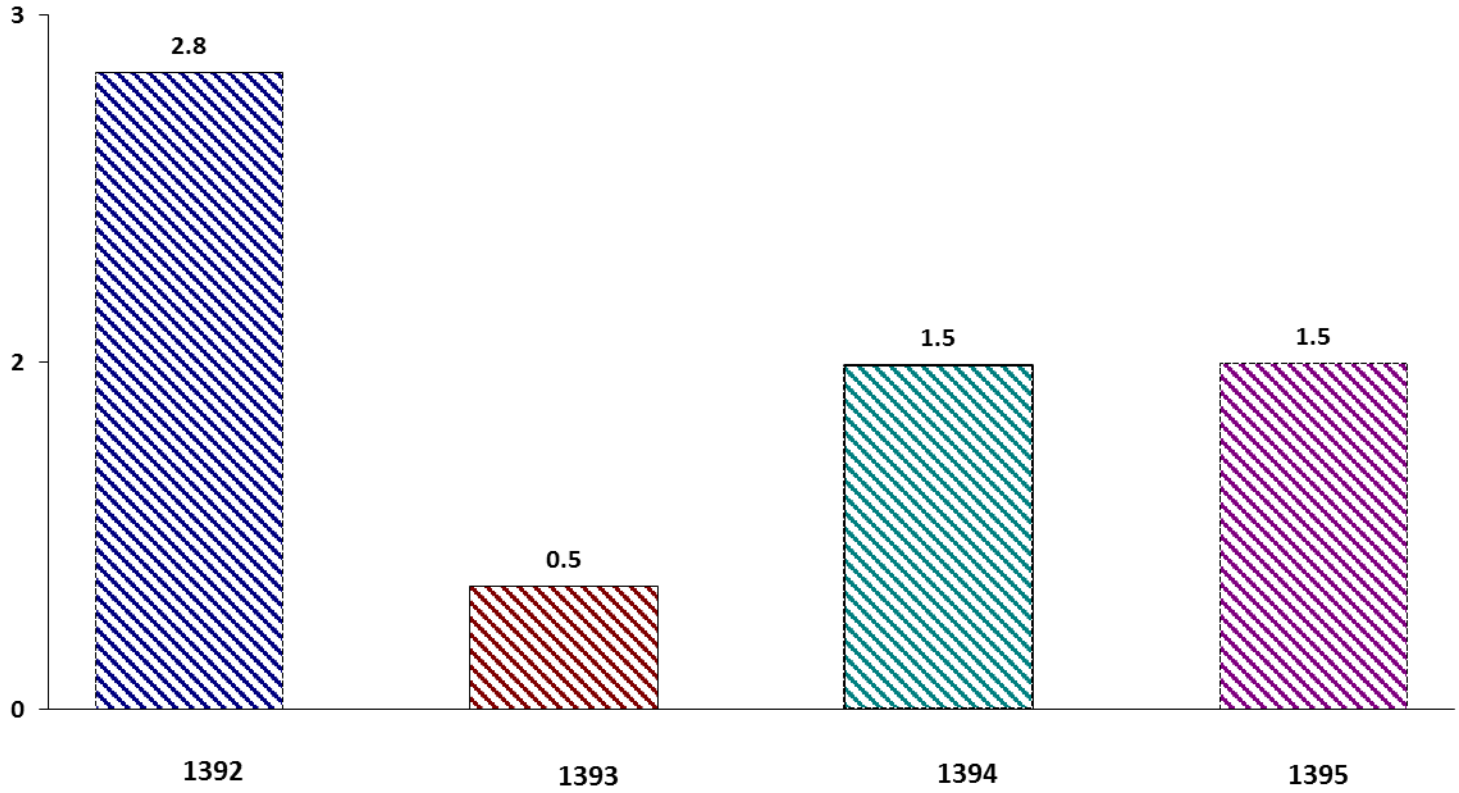
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در چهار محال بختياري(95-1392)



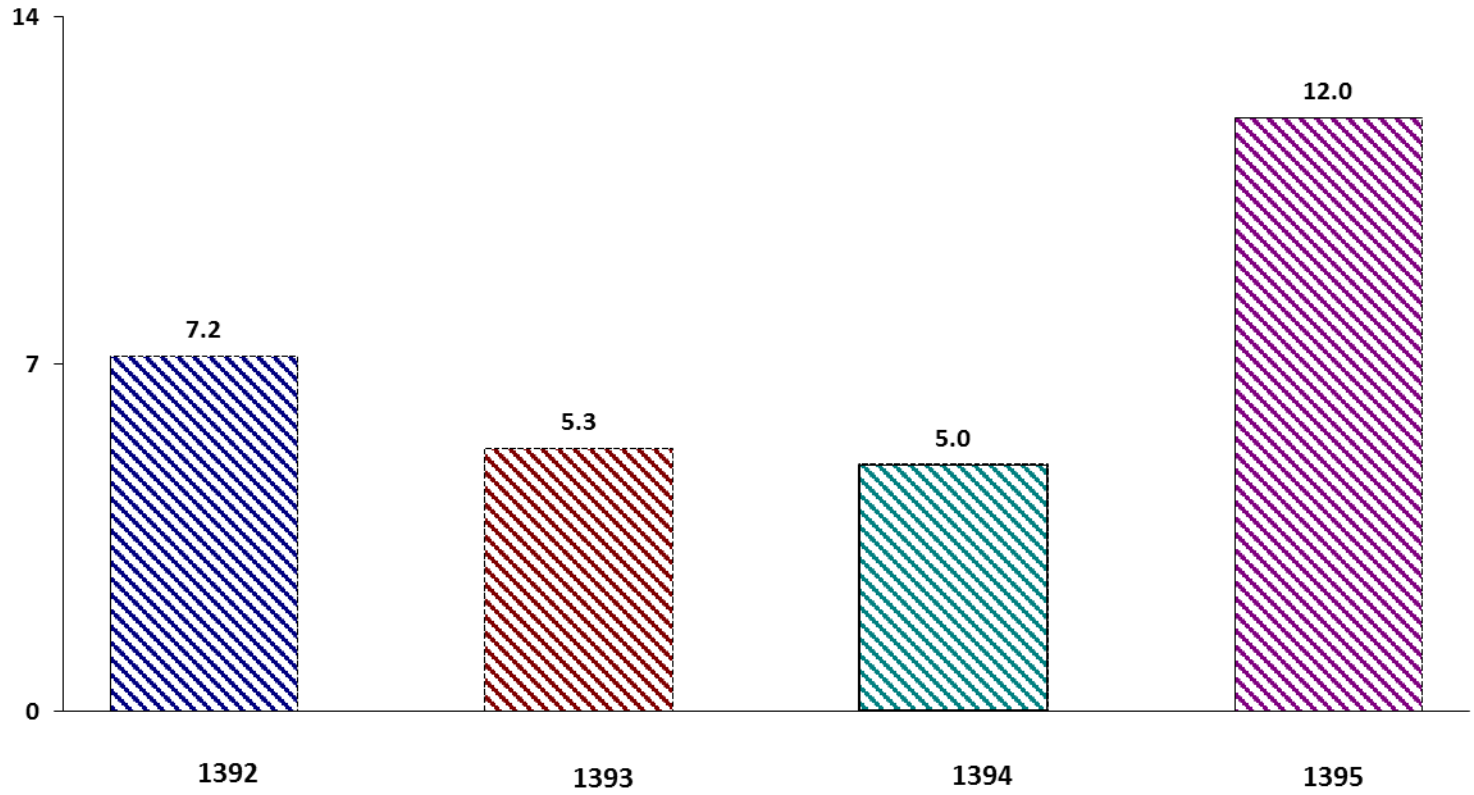
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در چهار محال بختياري(95-1392)



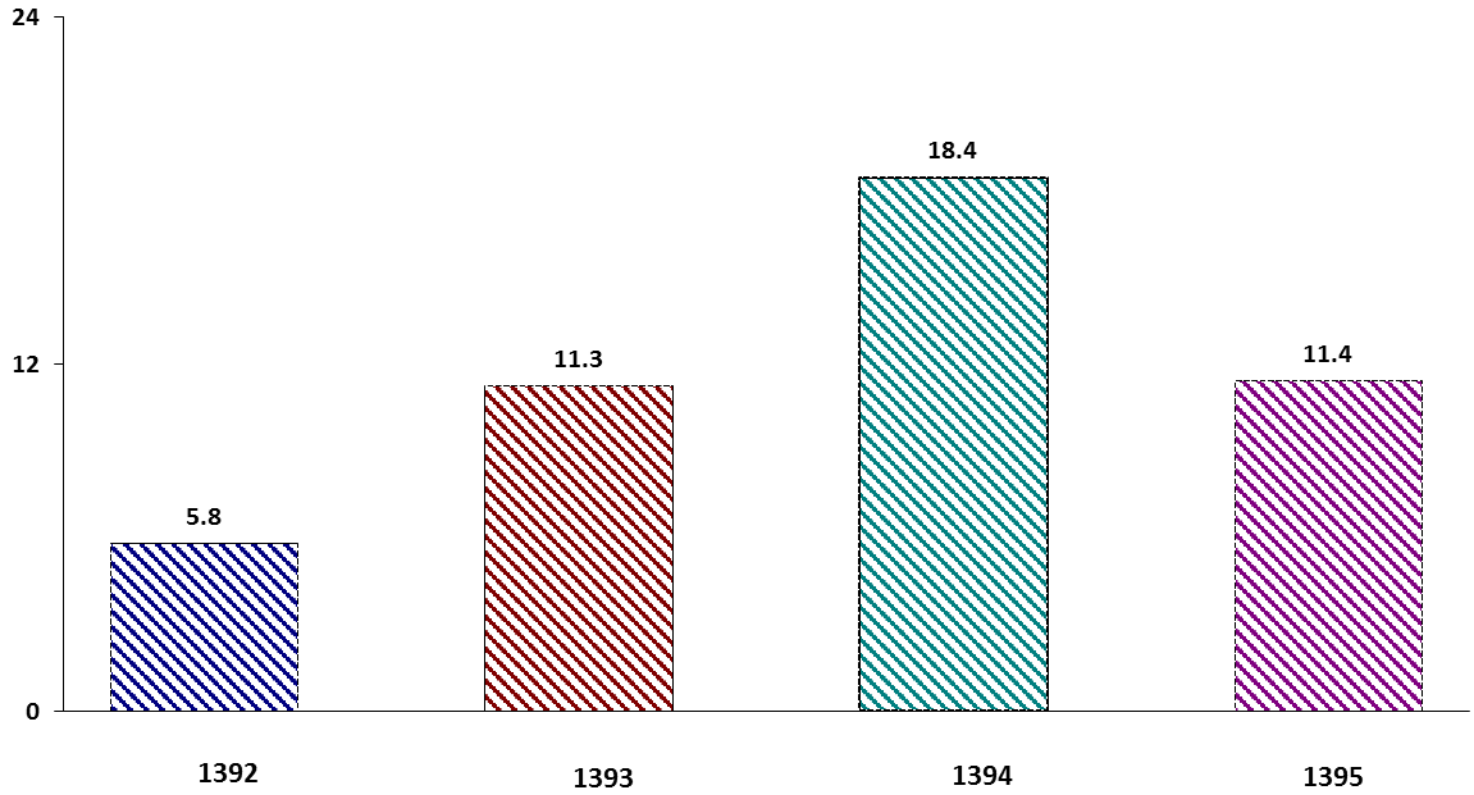
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در چهار محال بختياري(95-1392)



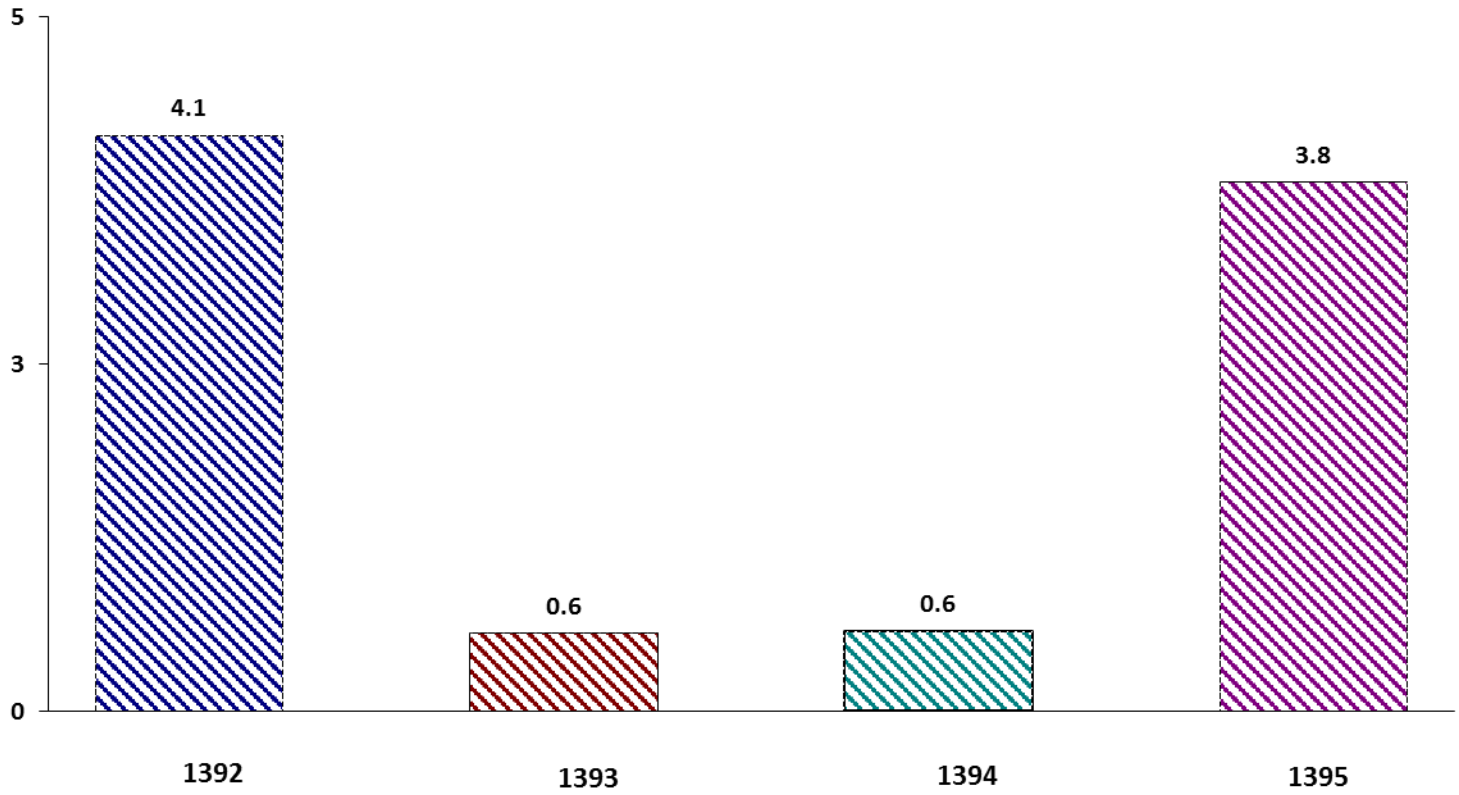
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در چهار محال بختیاري(95-1392)



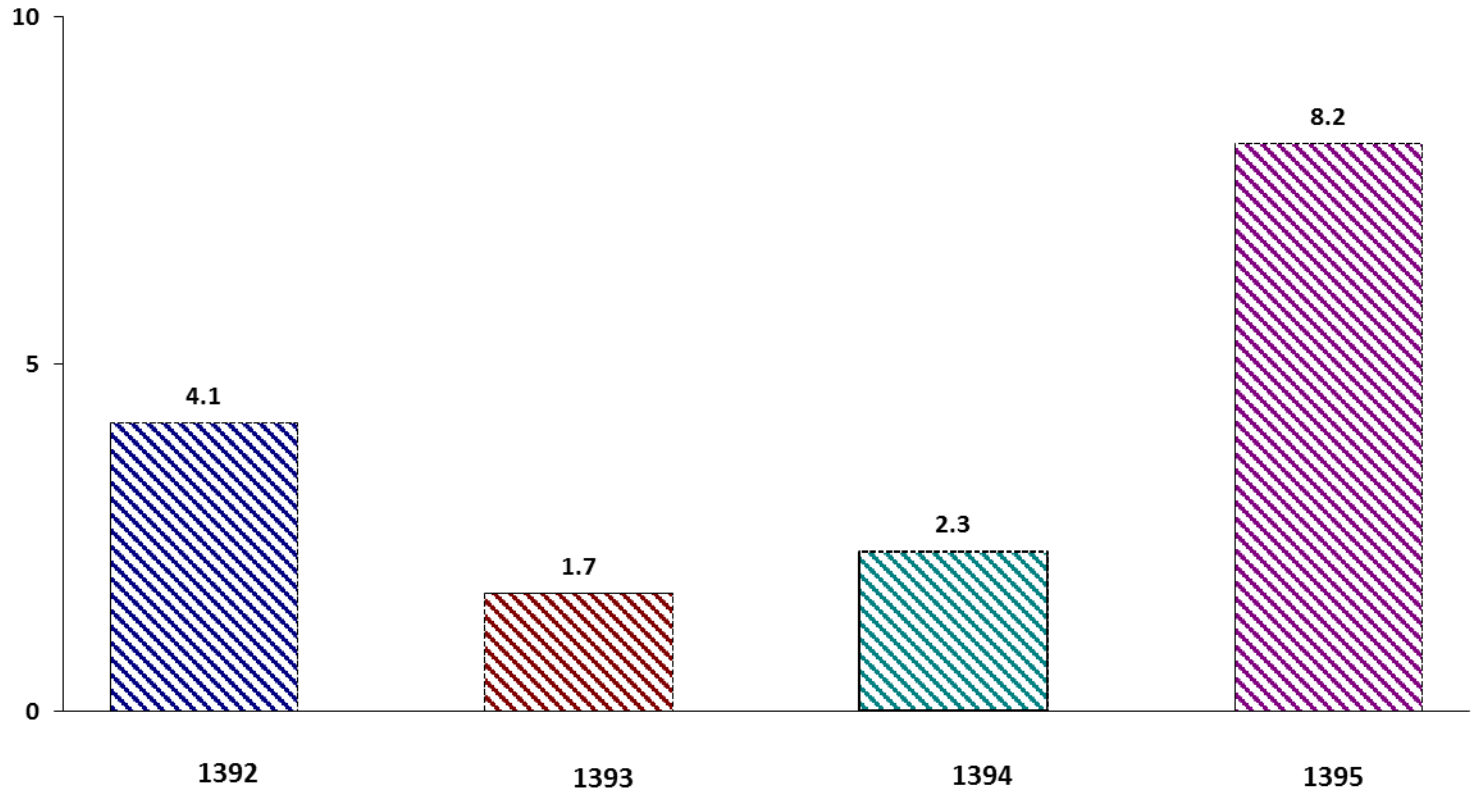
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در خراسان جنوبي(95-1392)



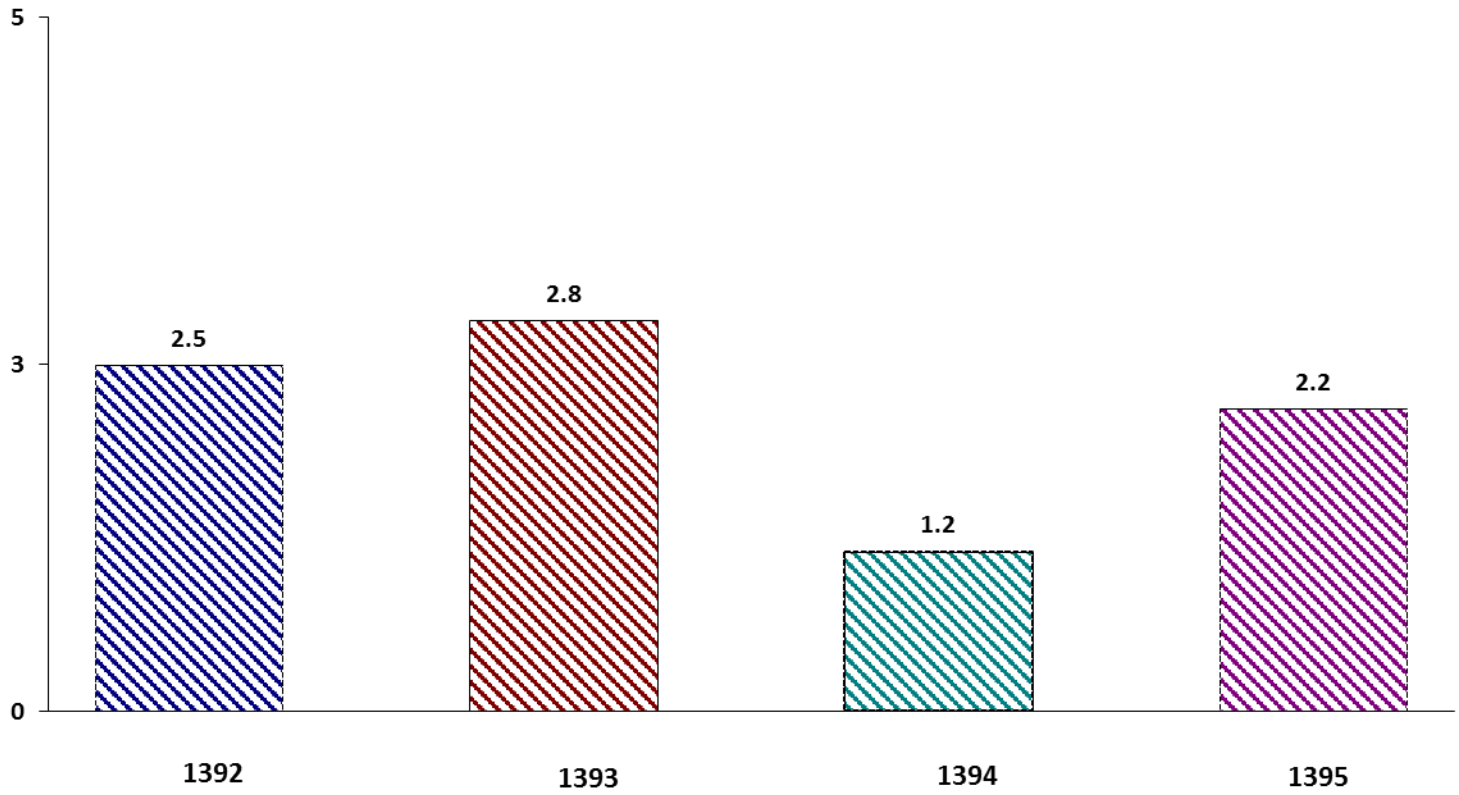
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در خراسان جنوبي(95-1392)



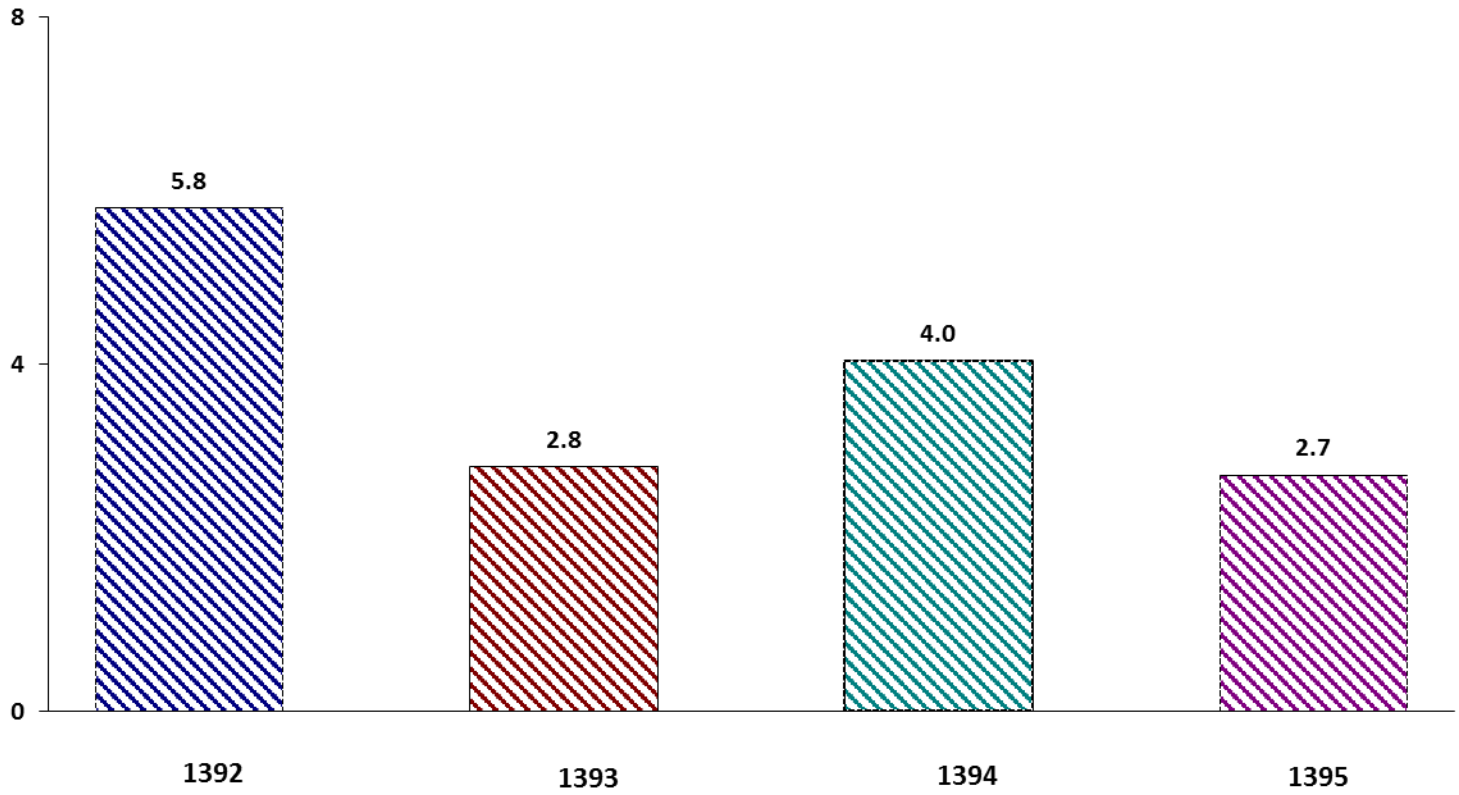
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در خراسان جنوبي(95-1392)



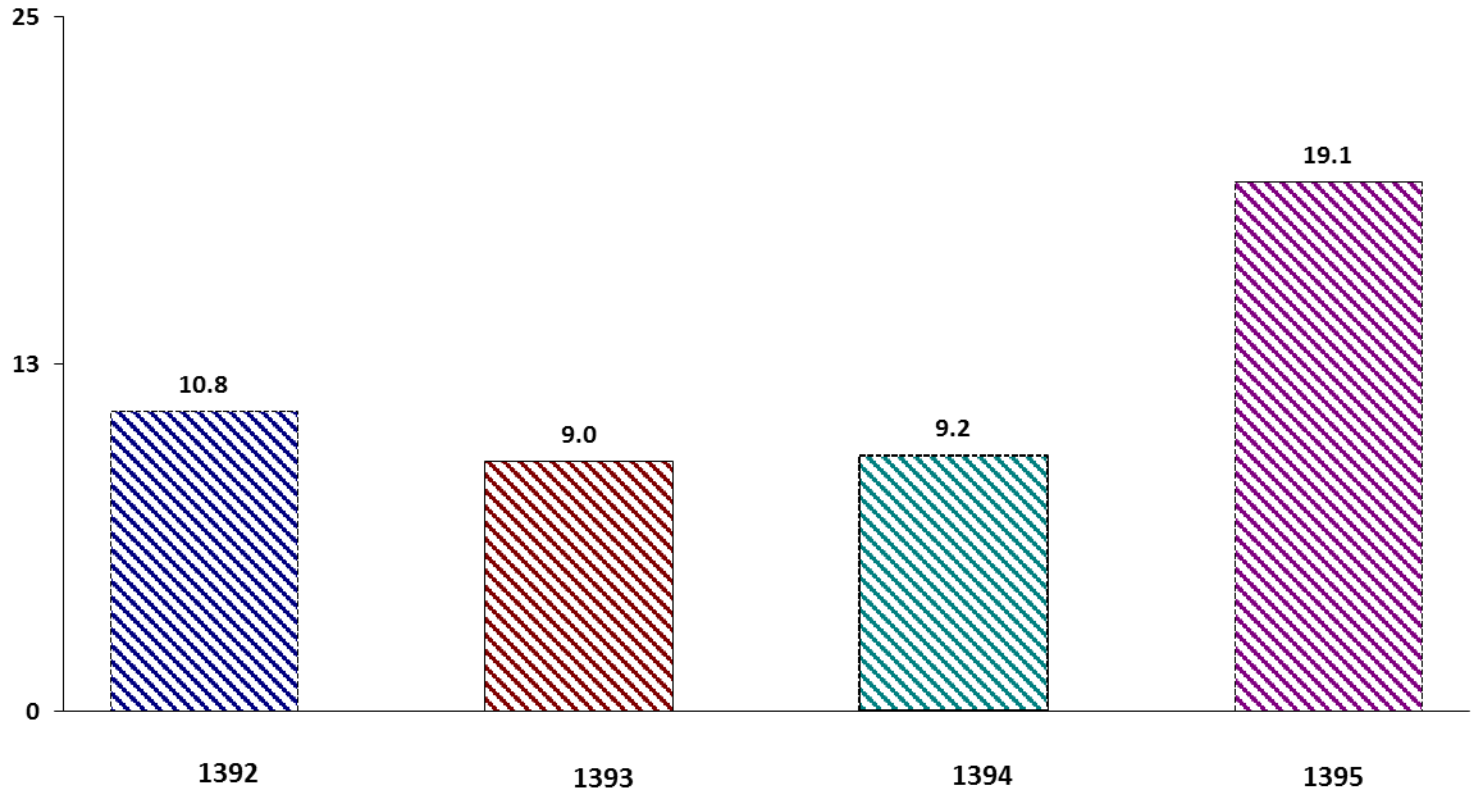
شیوع کلی ناهنجاری های مادرزادی قلبي هر ده هزار تولد) در خراسان جنوبي(95-1392)



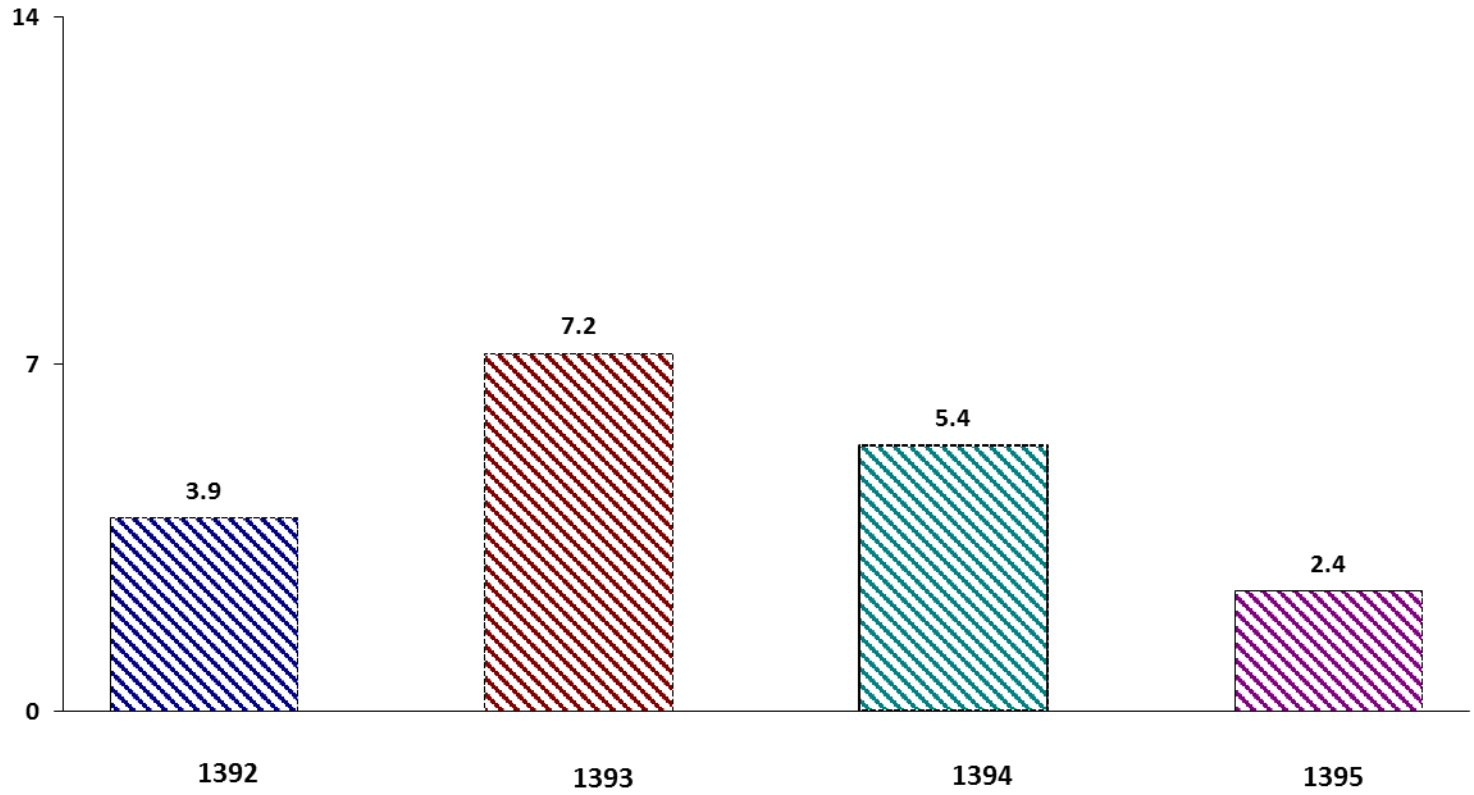
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در خراسان جنوبي(95-1392)



شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در خراسان جنوبي(95-1392)

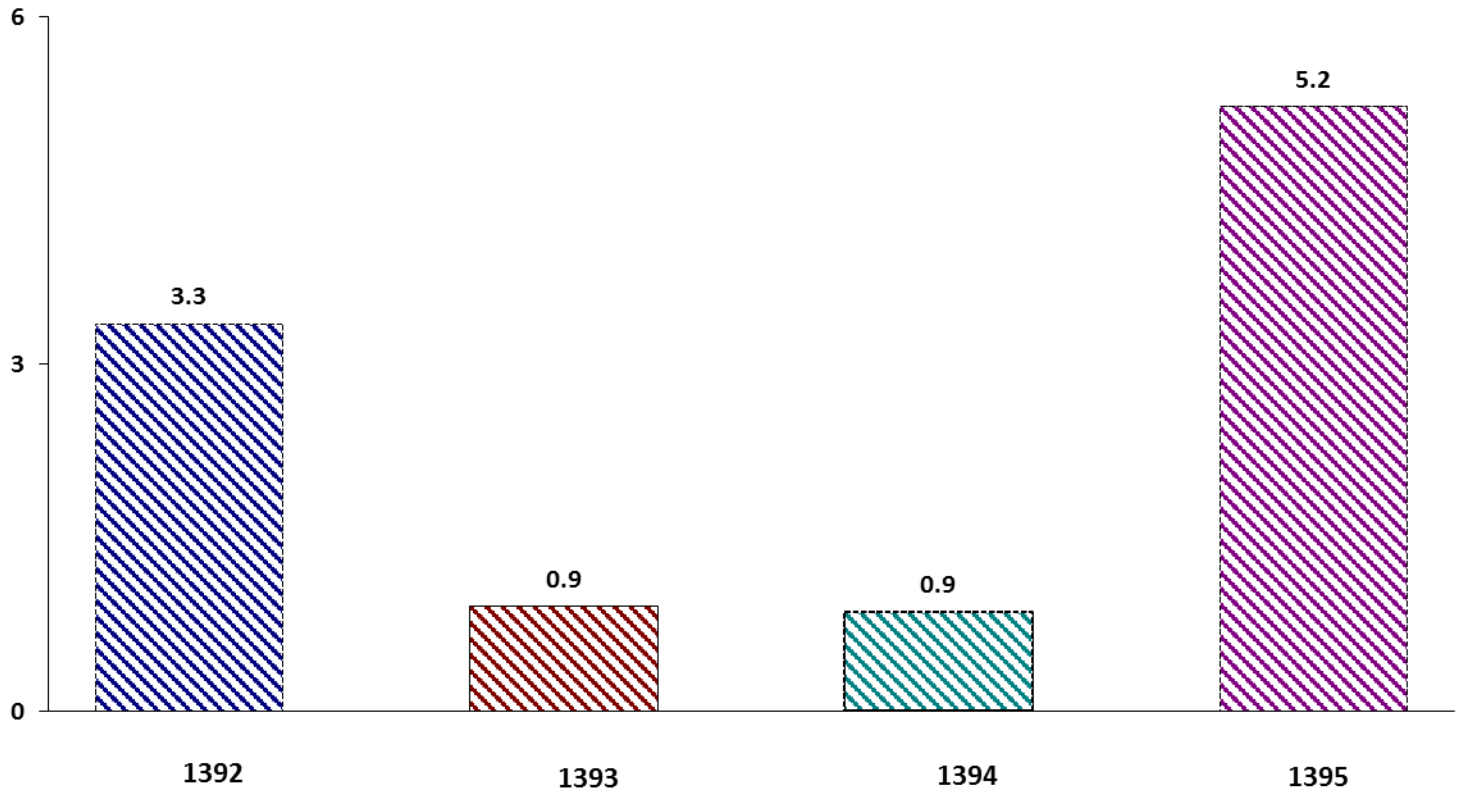


شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در خوزستان(95-1392)

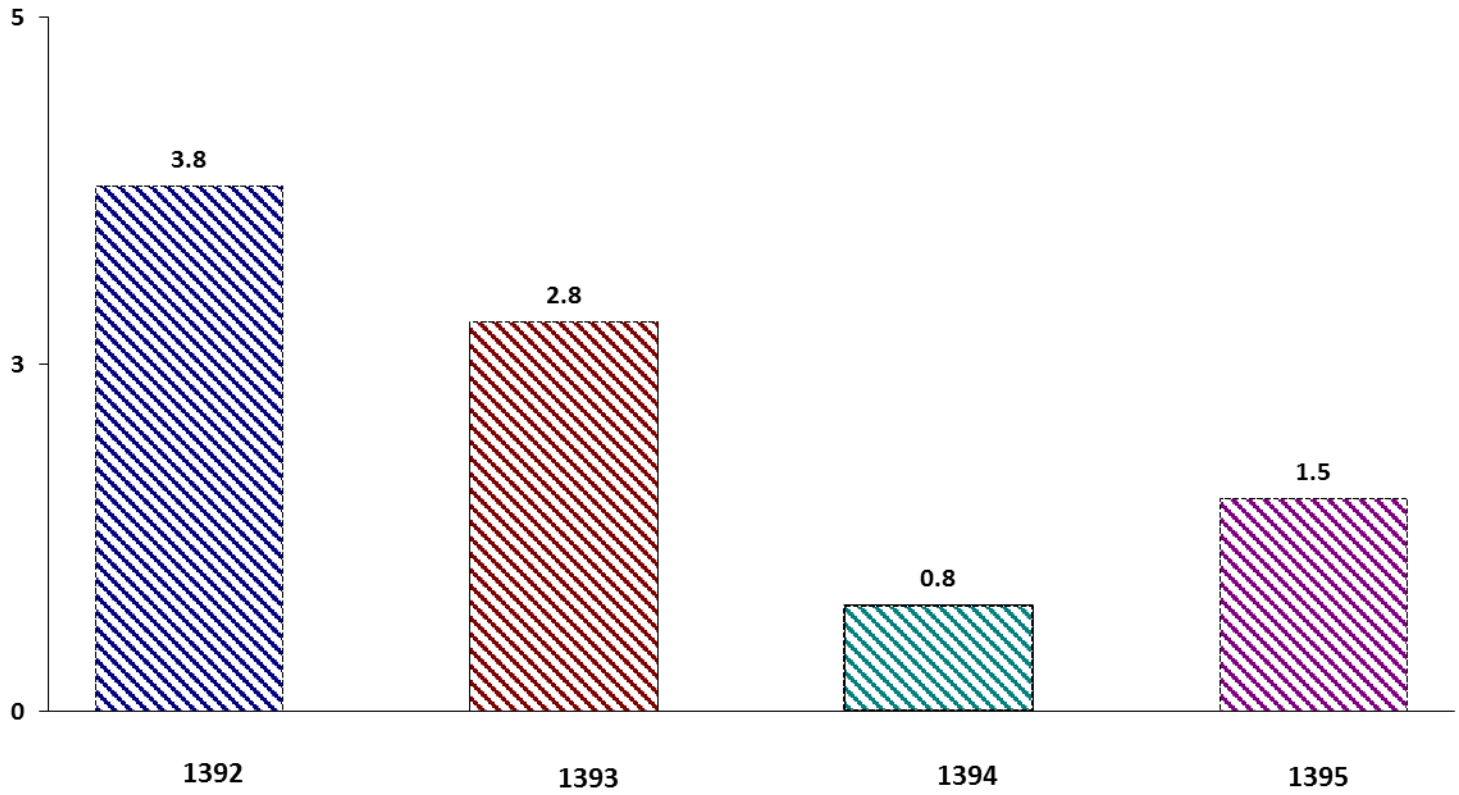


شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در خوزستان(95-1392)

شیوع کلی ناهنجاری های مادرزادی اسکلتي و عضلاني(در هر ده هزار تولد) در خوزستان(95-1392)

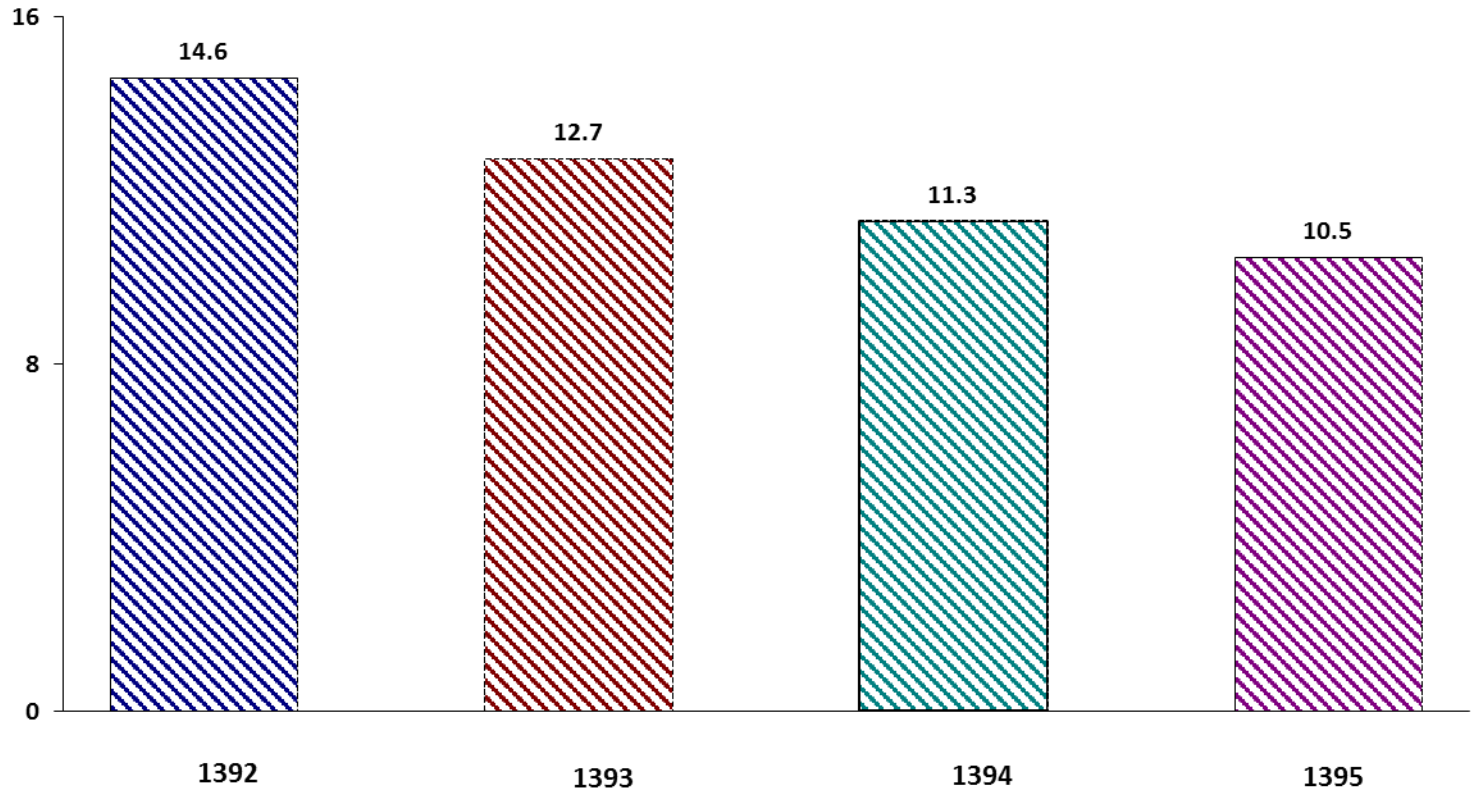


شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در خوزستان(95-1392)

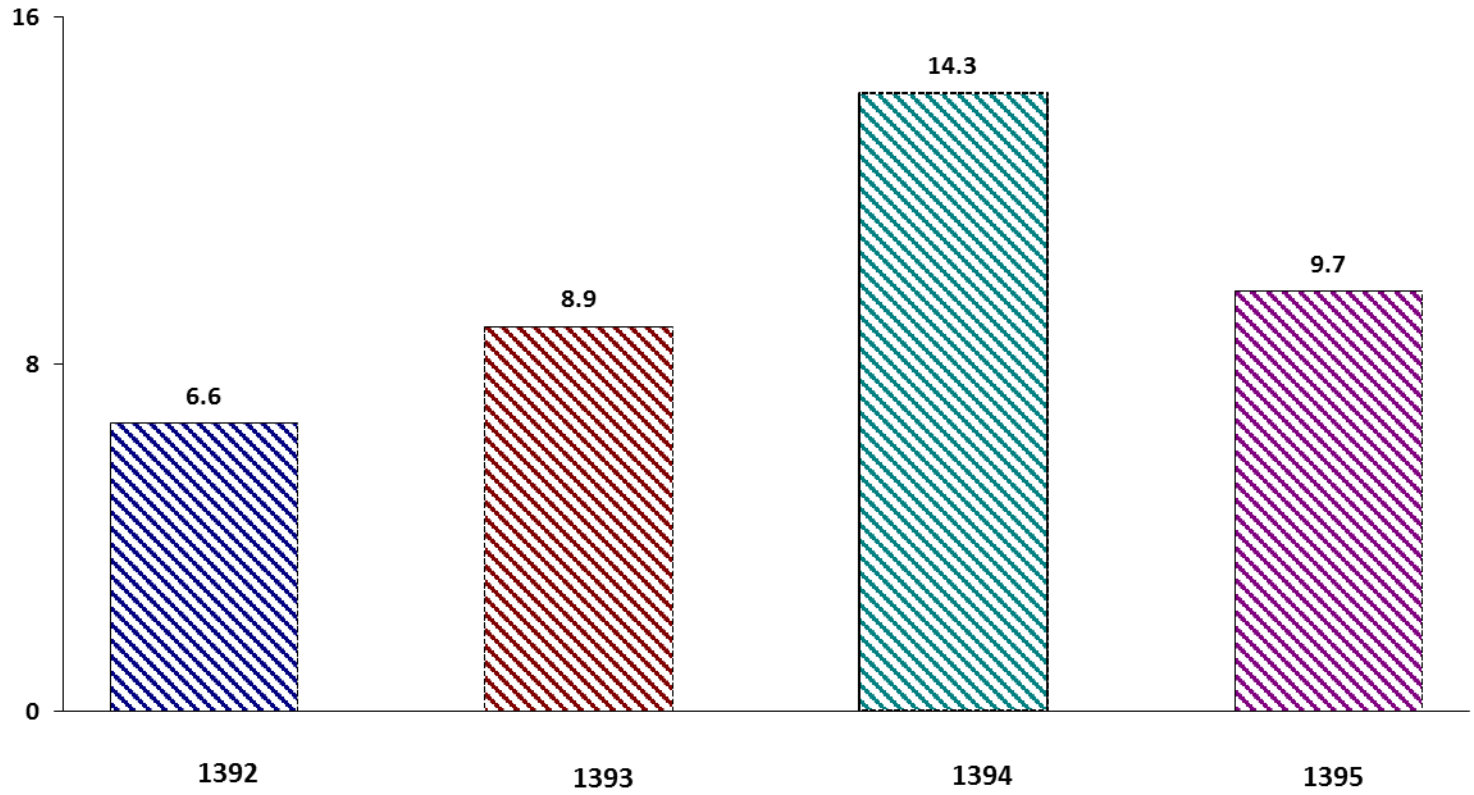


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در خوزستان(95-1392)

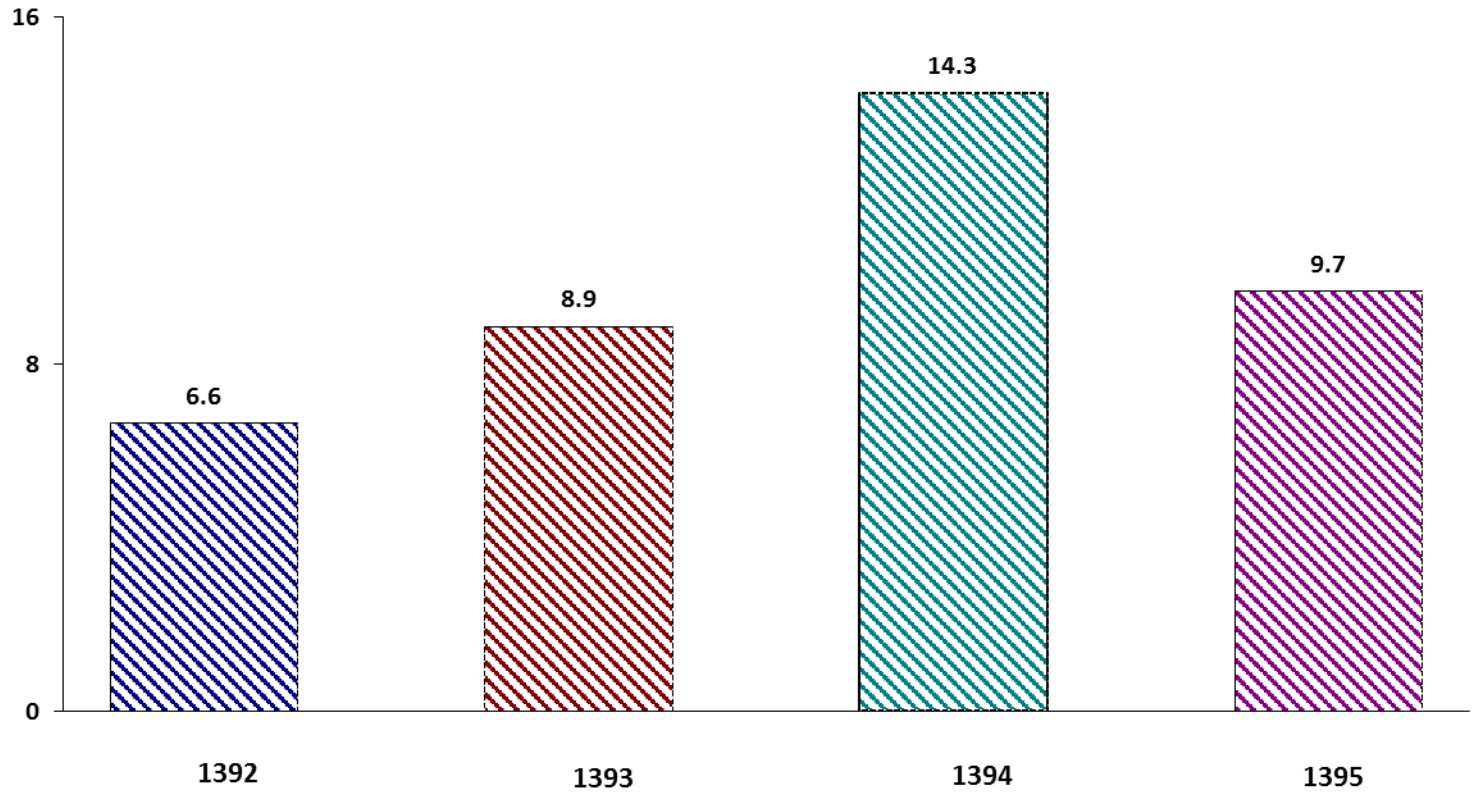
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در خوزستان(95-1392)



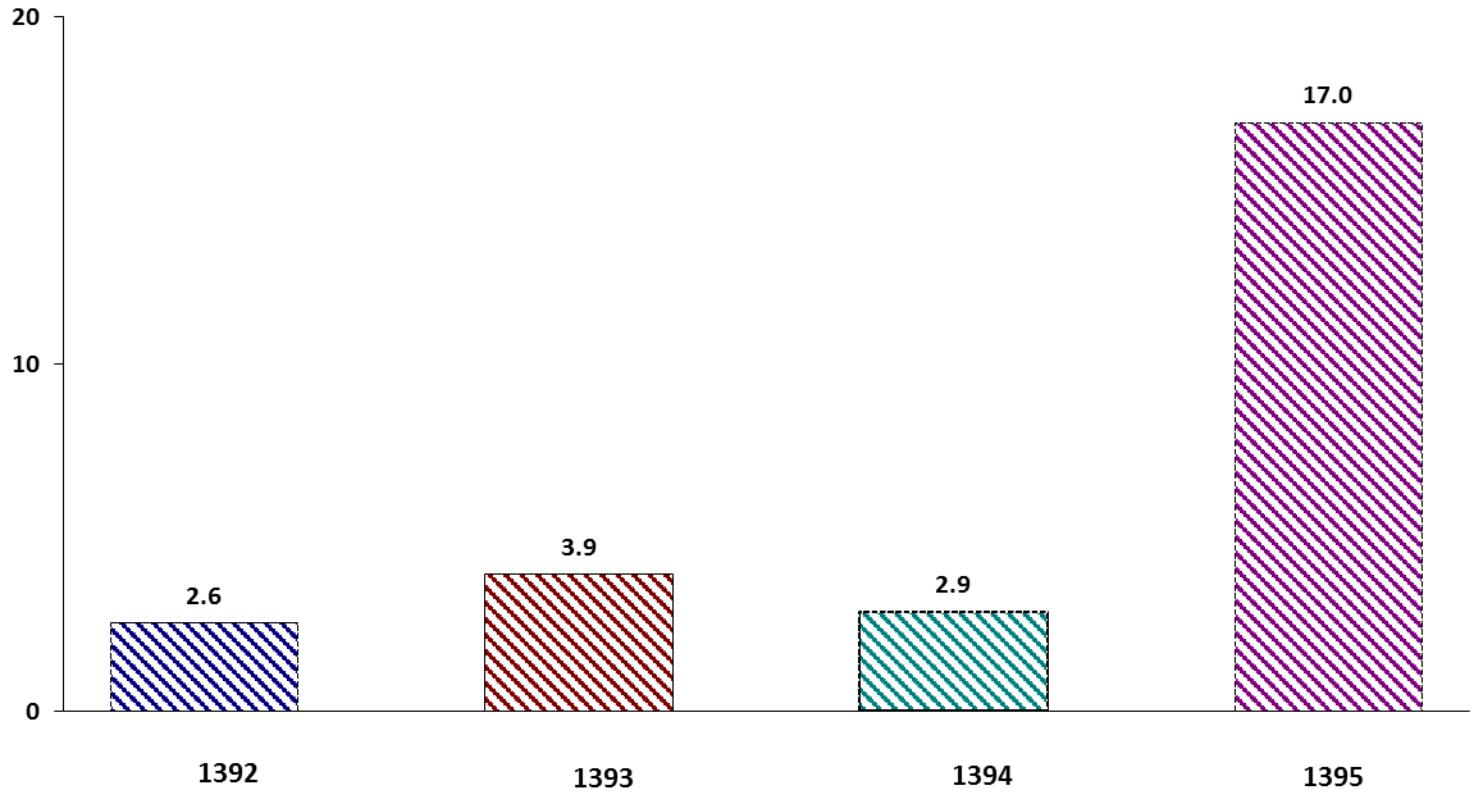
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در زنجان(95-1392)



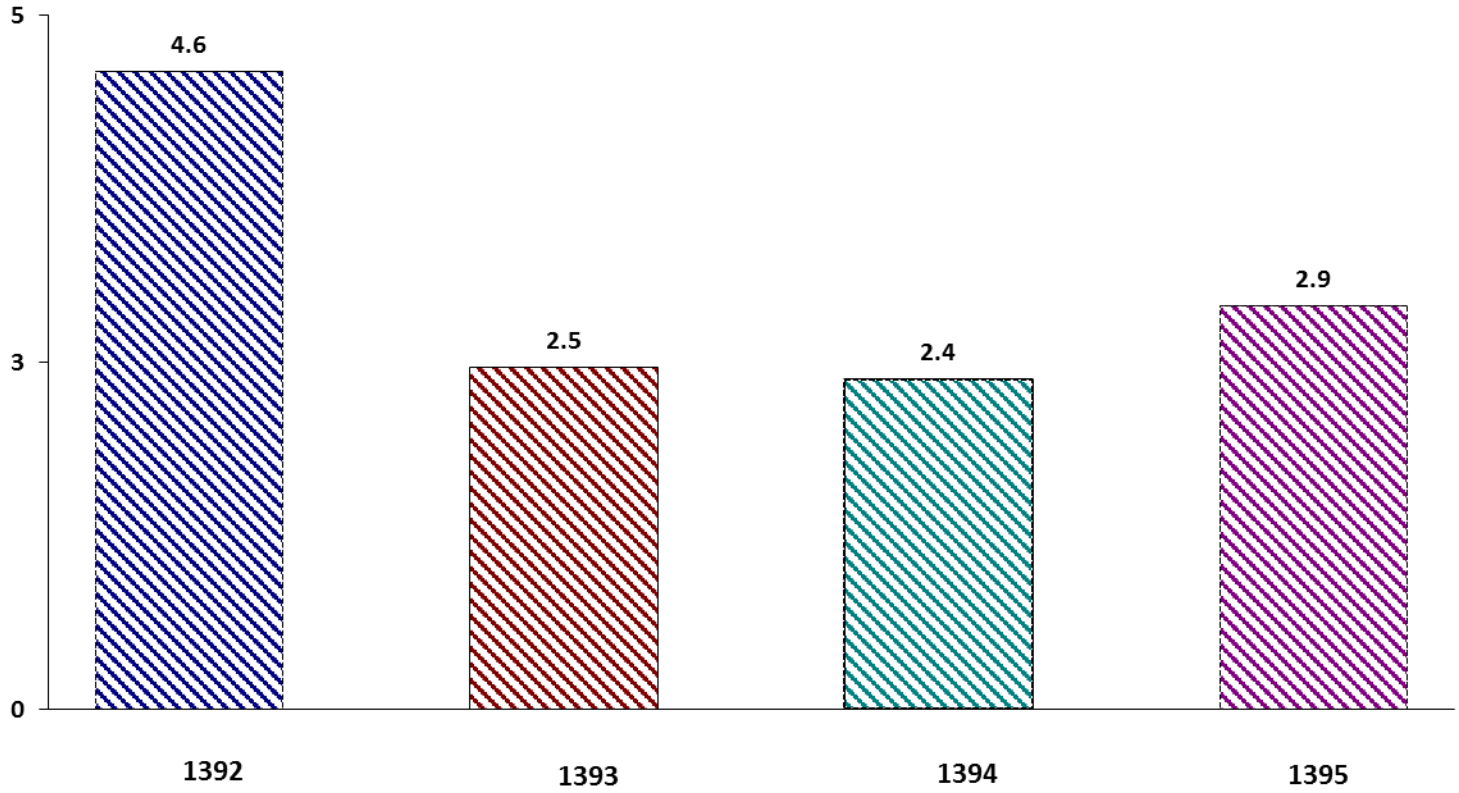
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در زنجان(95-1392)



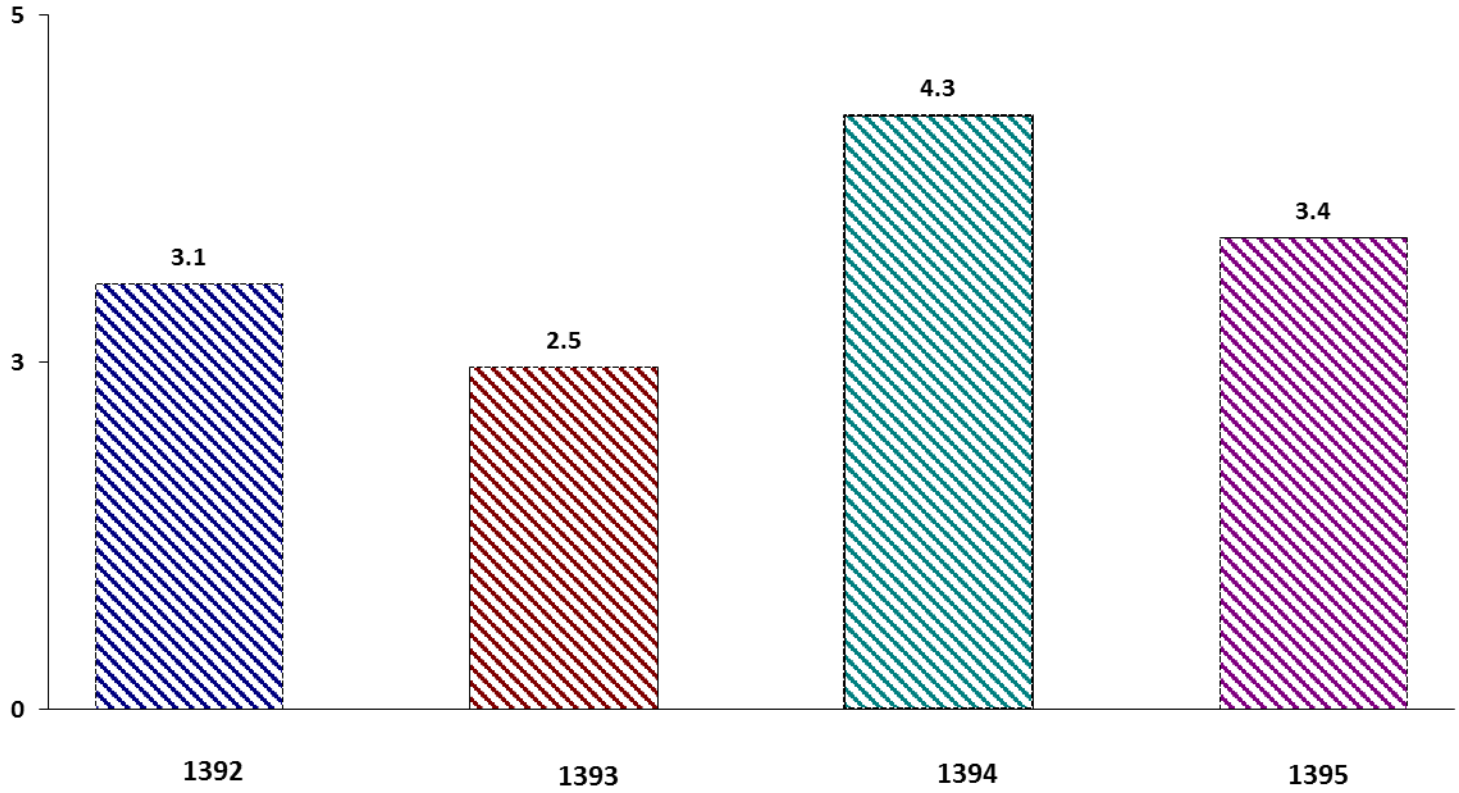
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در زنجان(95-1392)



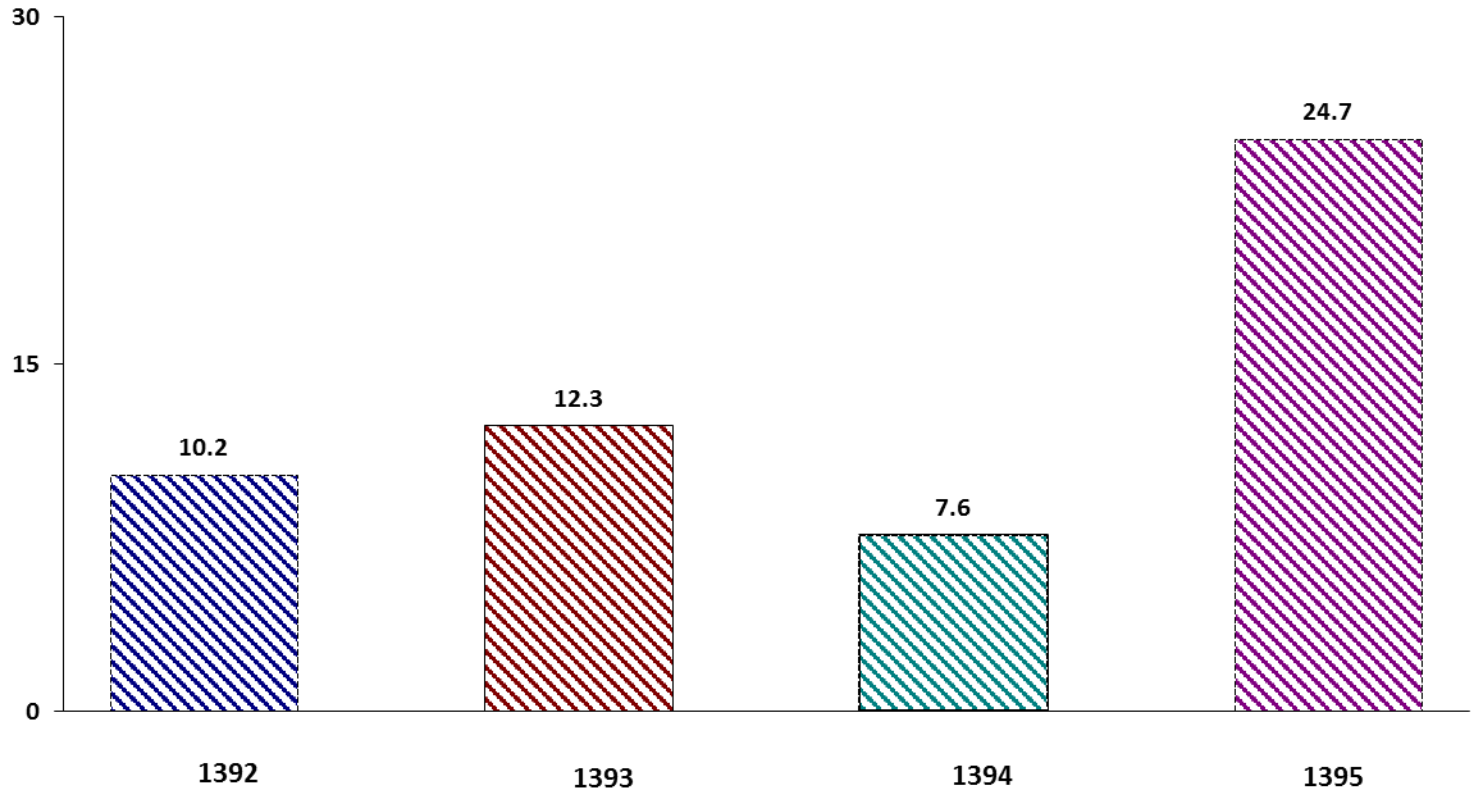
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در زنجان(95-1392)



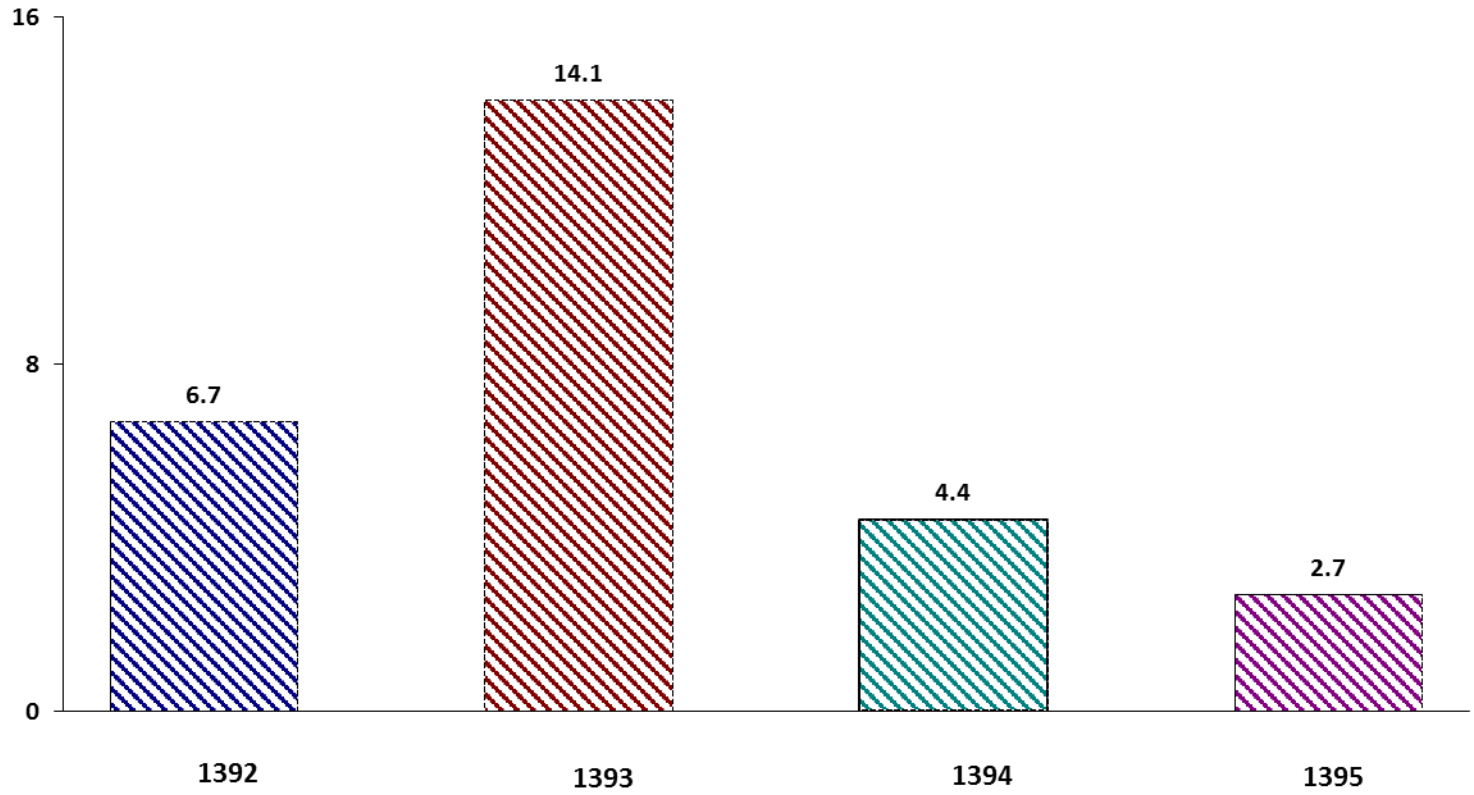
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در زنجان(95-1392)



شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در زنجان(95-1392)

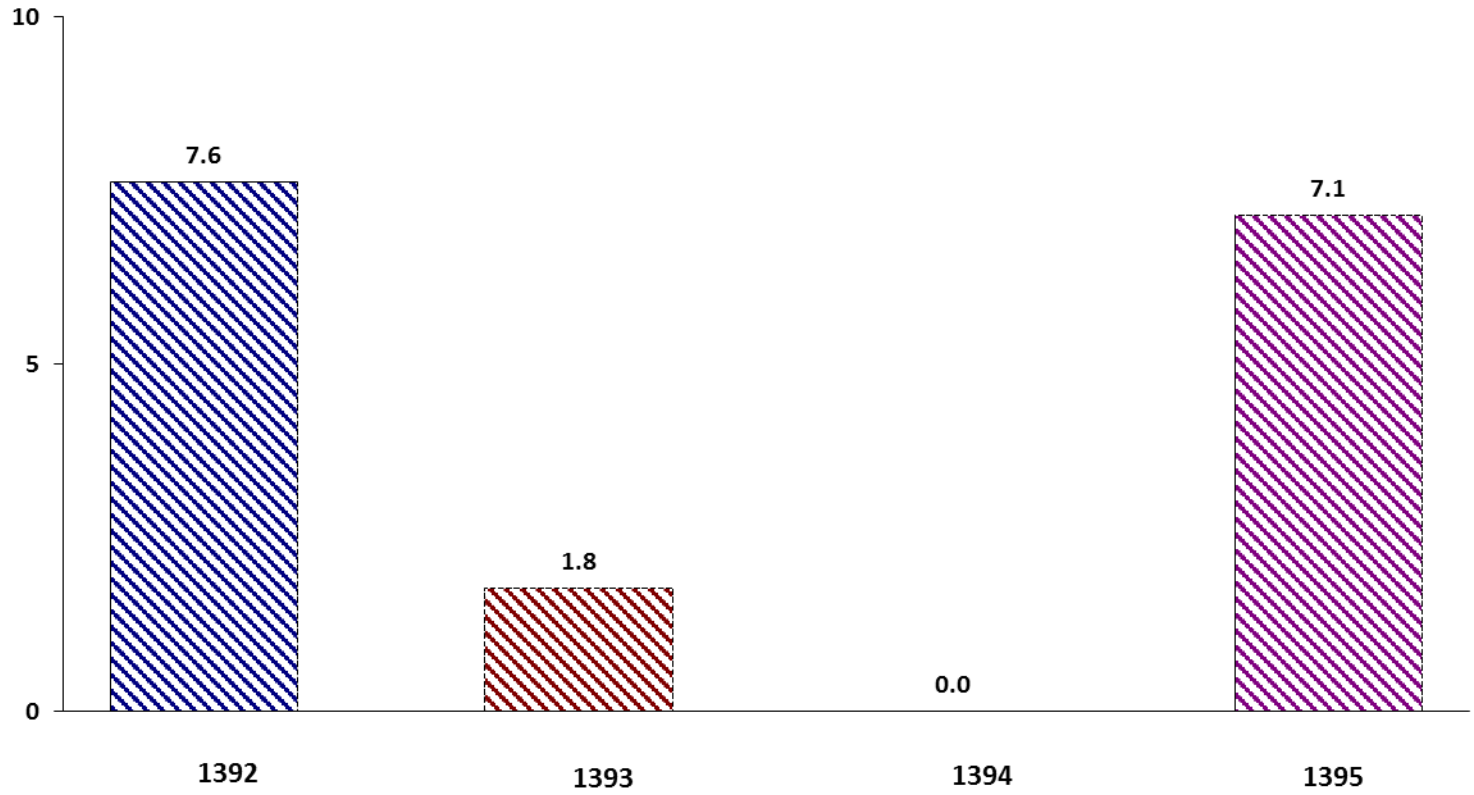


شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در سمنان(95-1392)

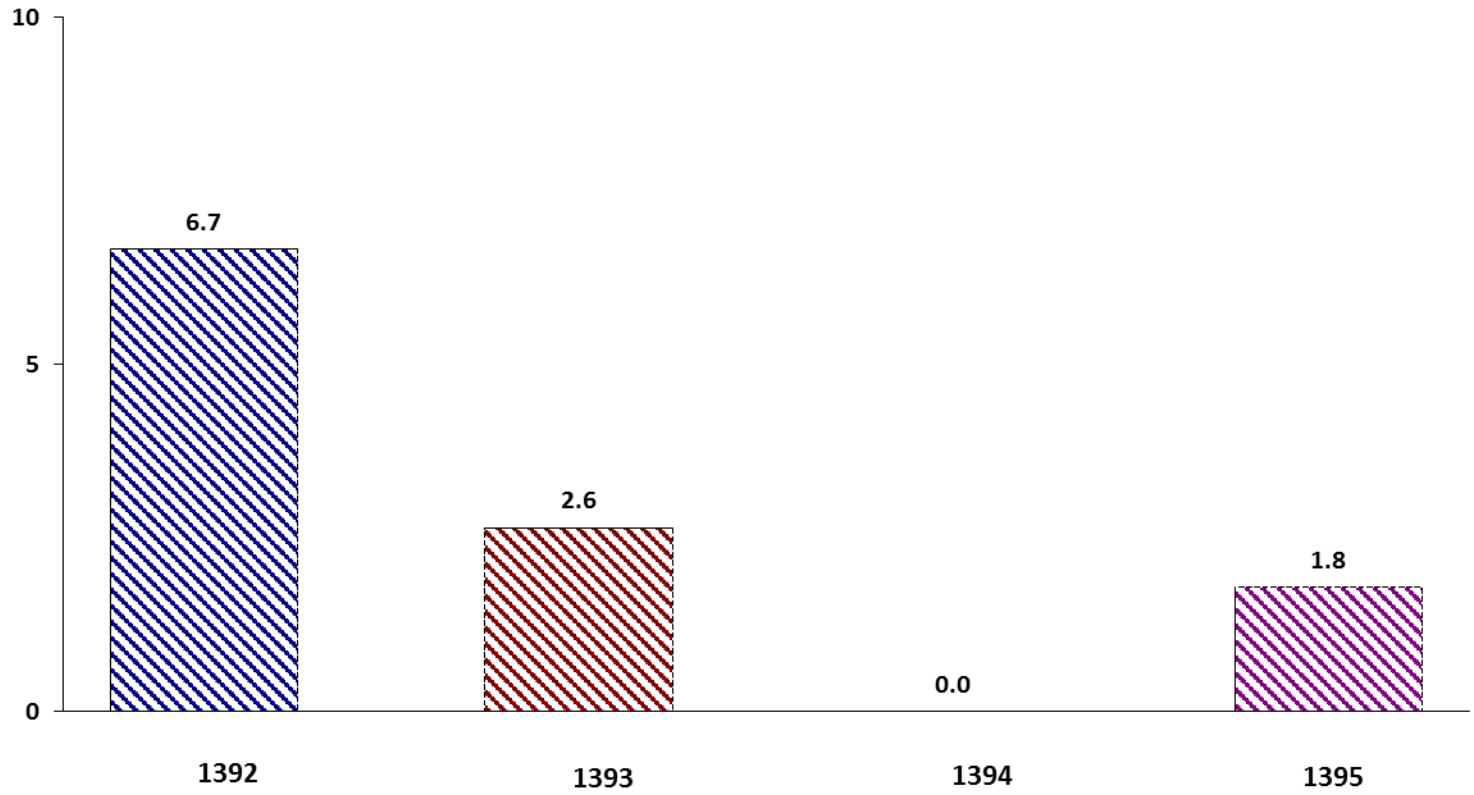


شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در سمنان(95-1392)

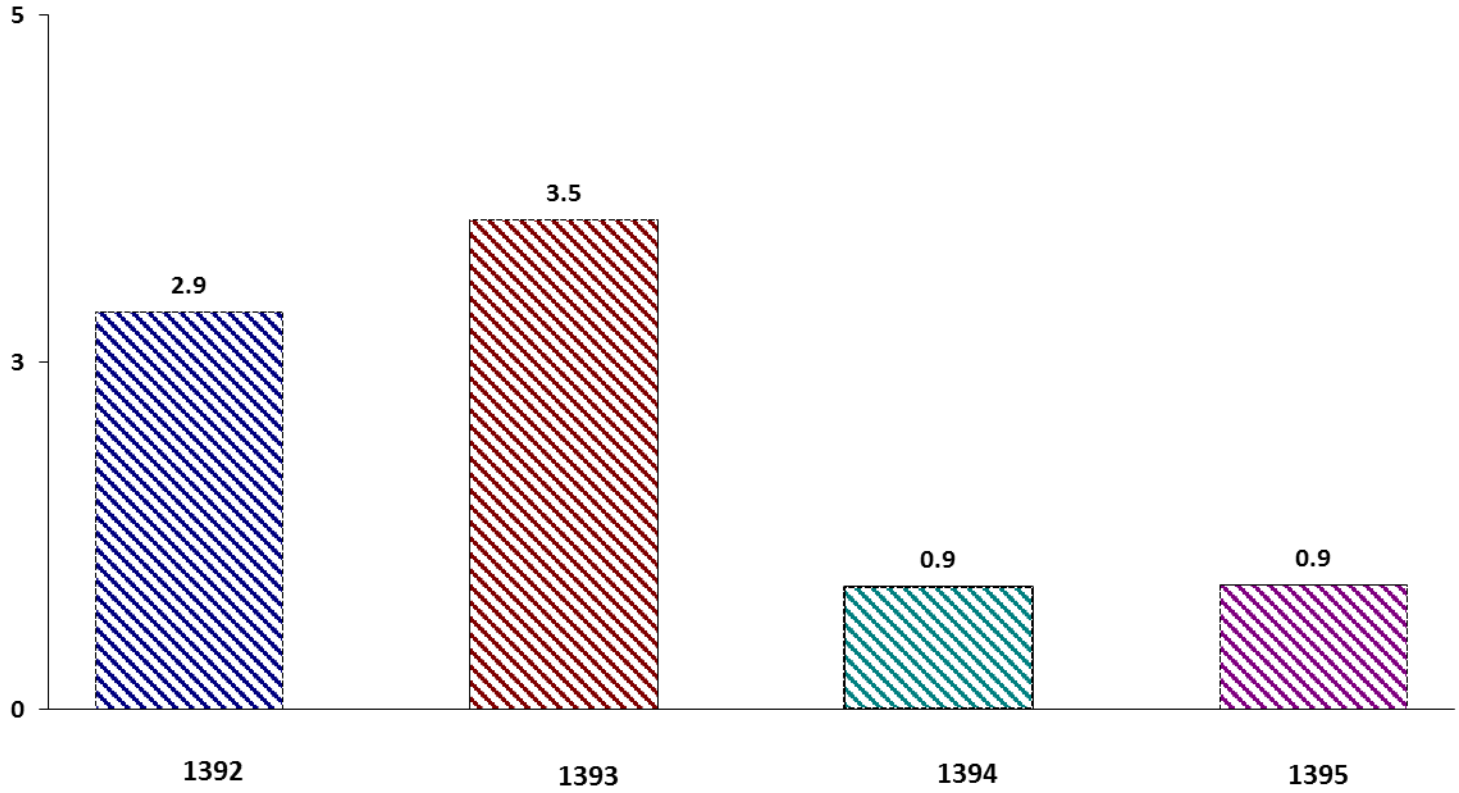
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسكلتي(در هر ده هزار تولد) در سمنان(95-1392)



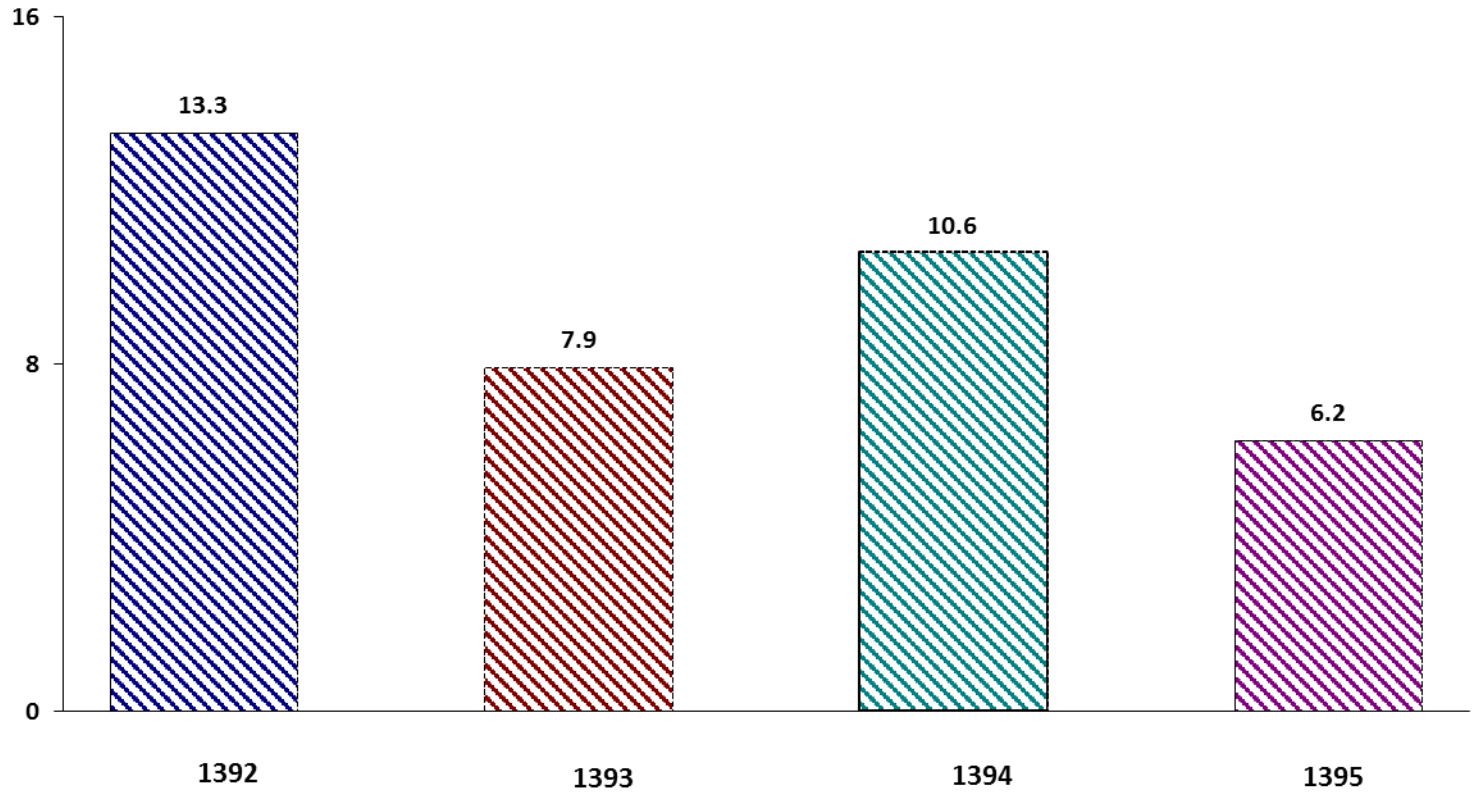
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در سمنان(95-1392)



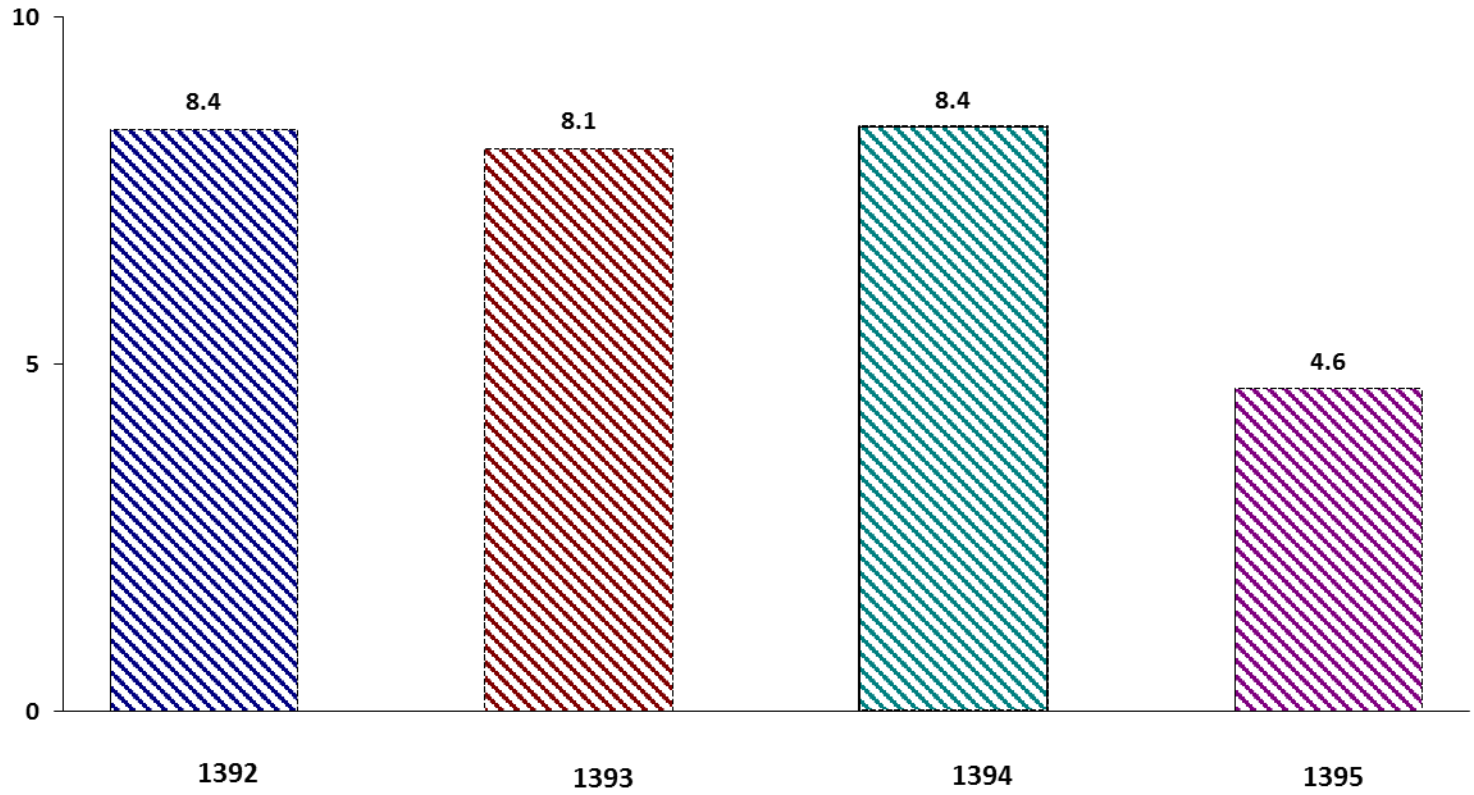
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در سمنان(95-1392)



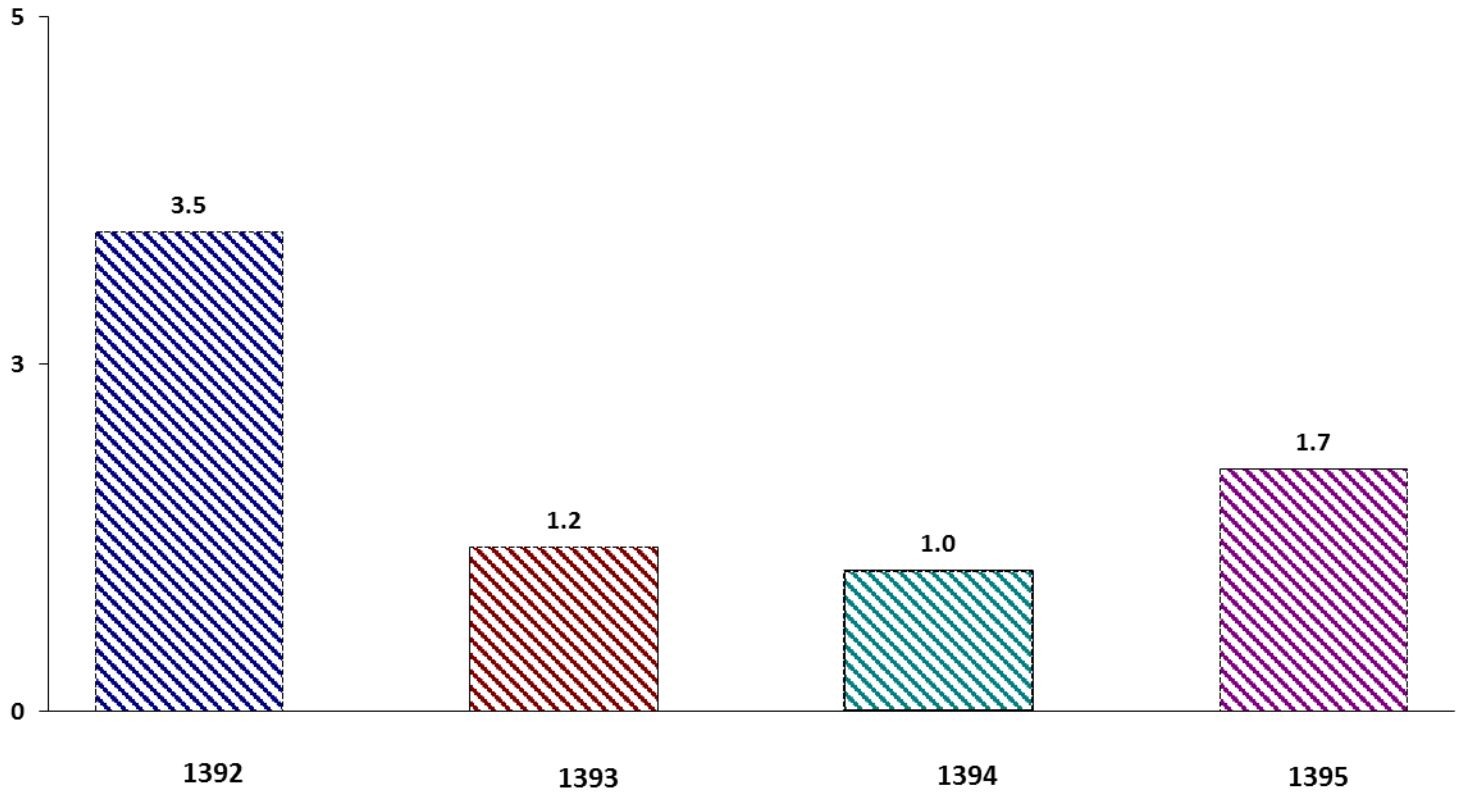
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در سمنان(95-1392)



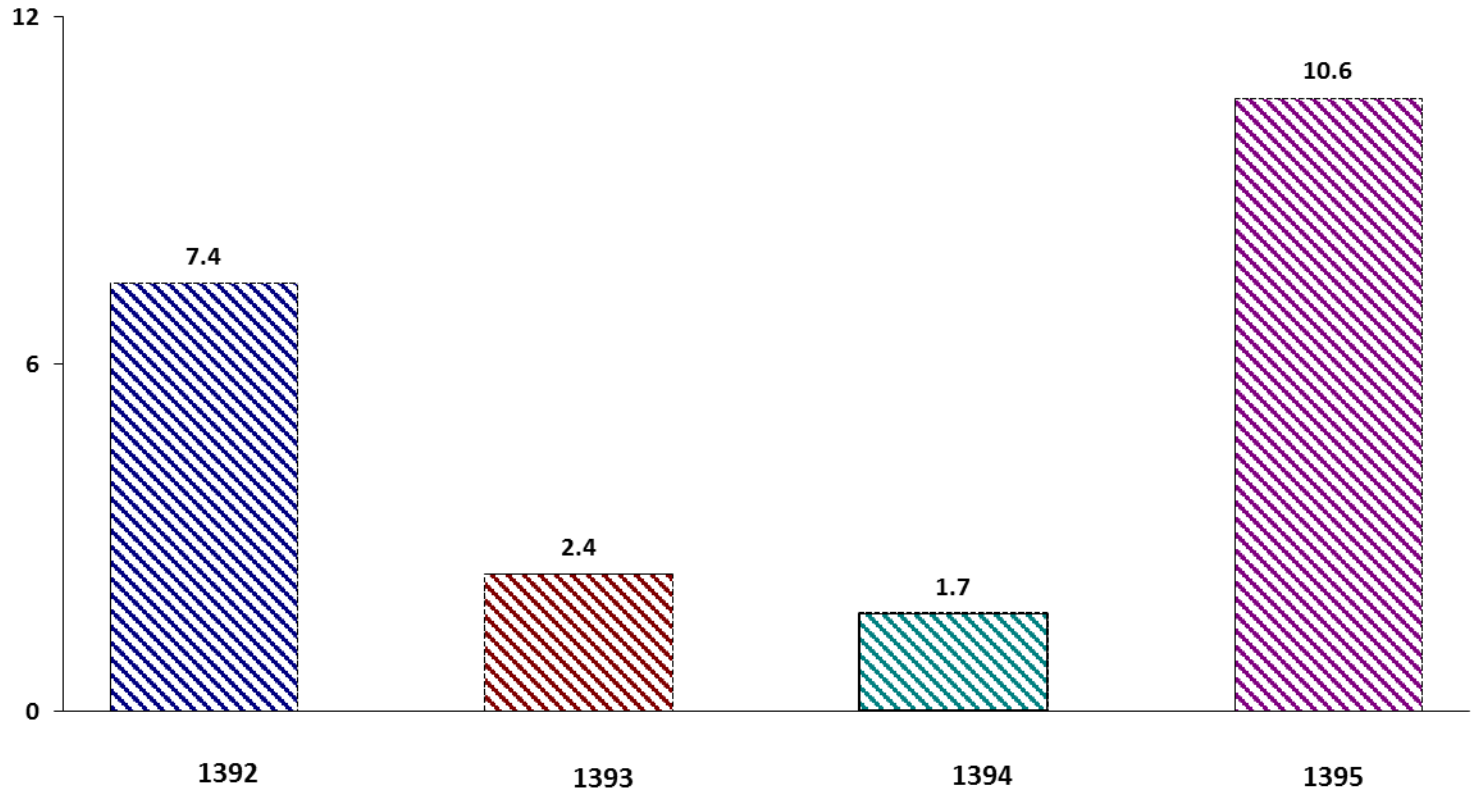
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در سیستان و بلوچستان(95-1392)



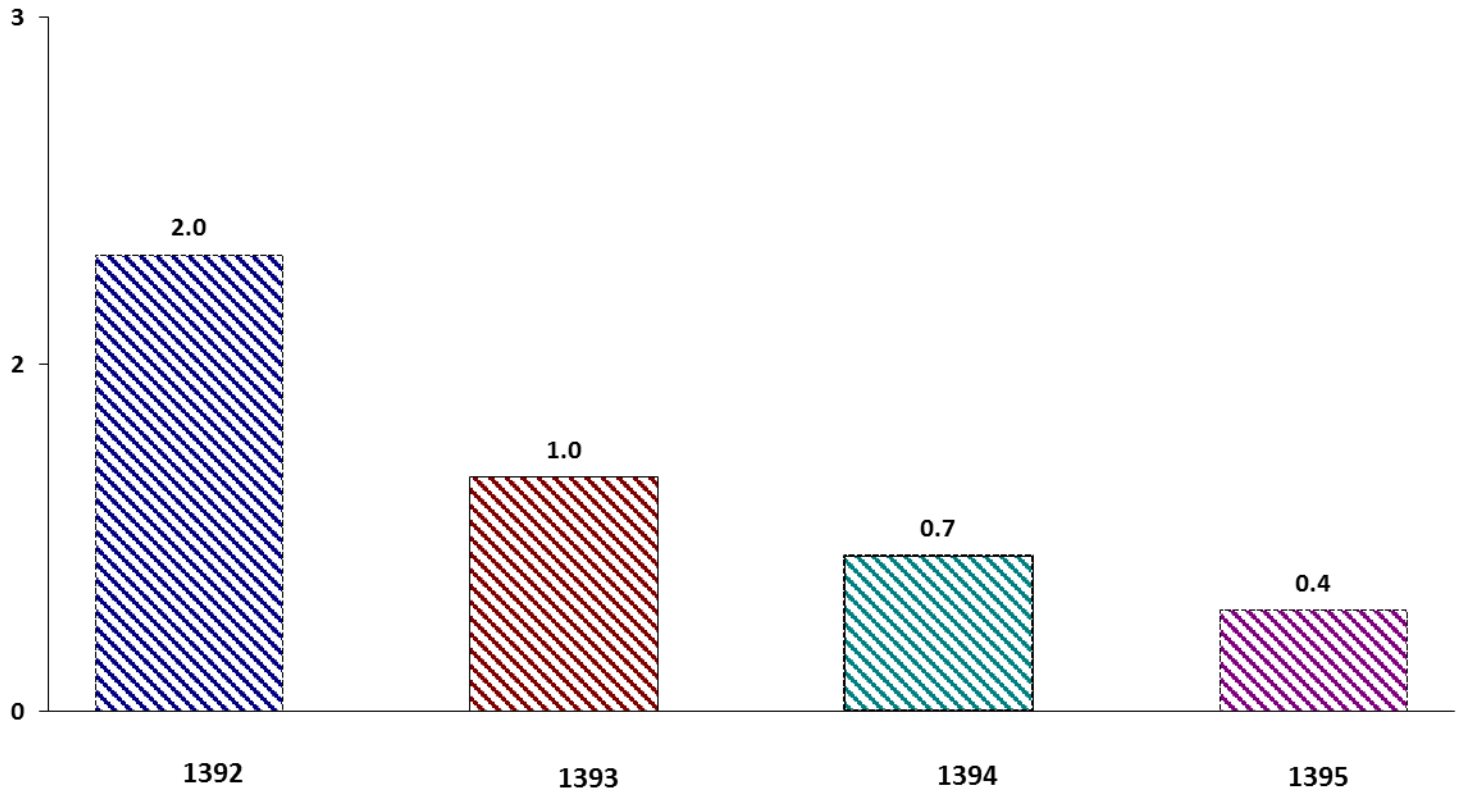
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در سیستان و بلوچستان(95-1392)



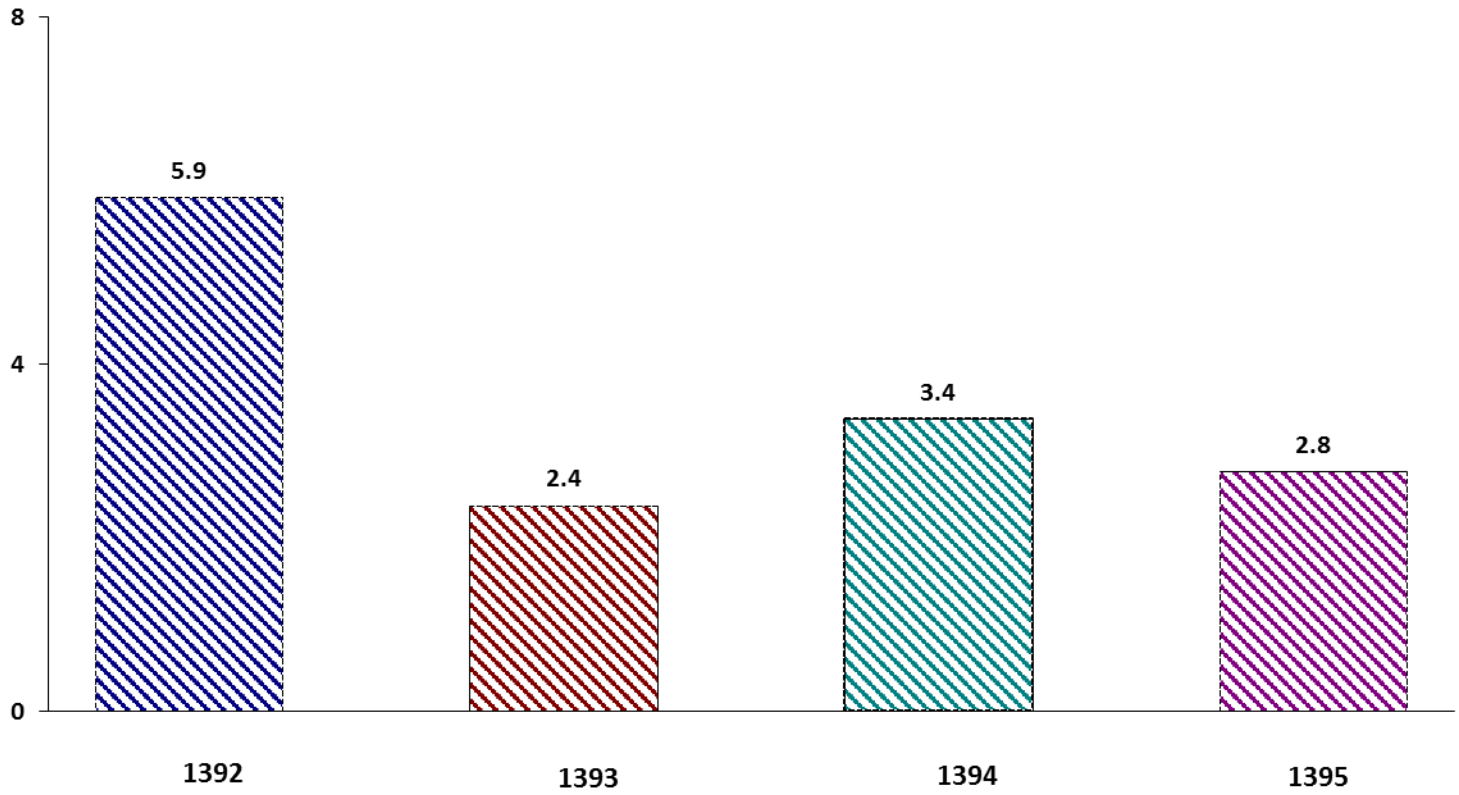
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در سیستان و بلوچستان(95-1392)



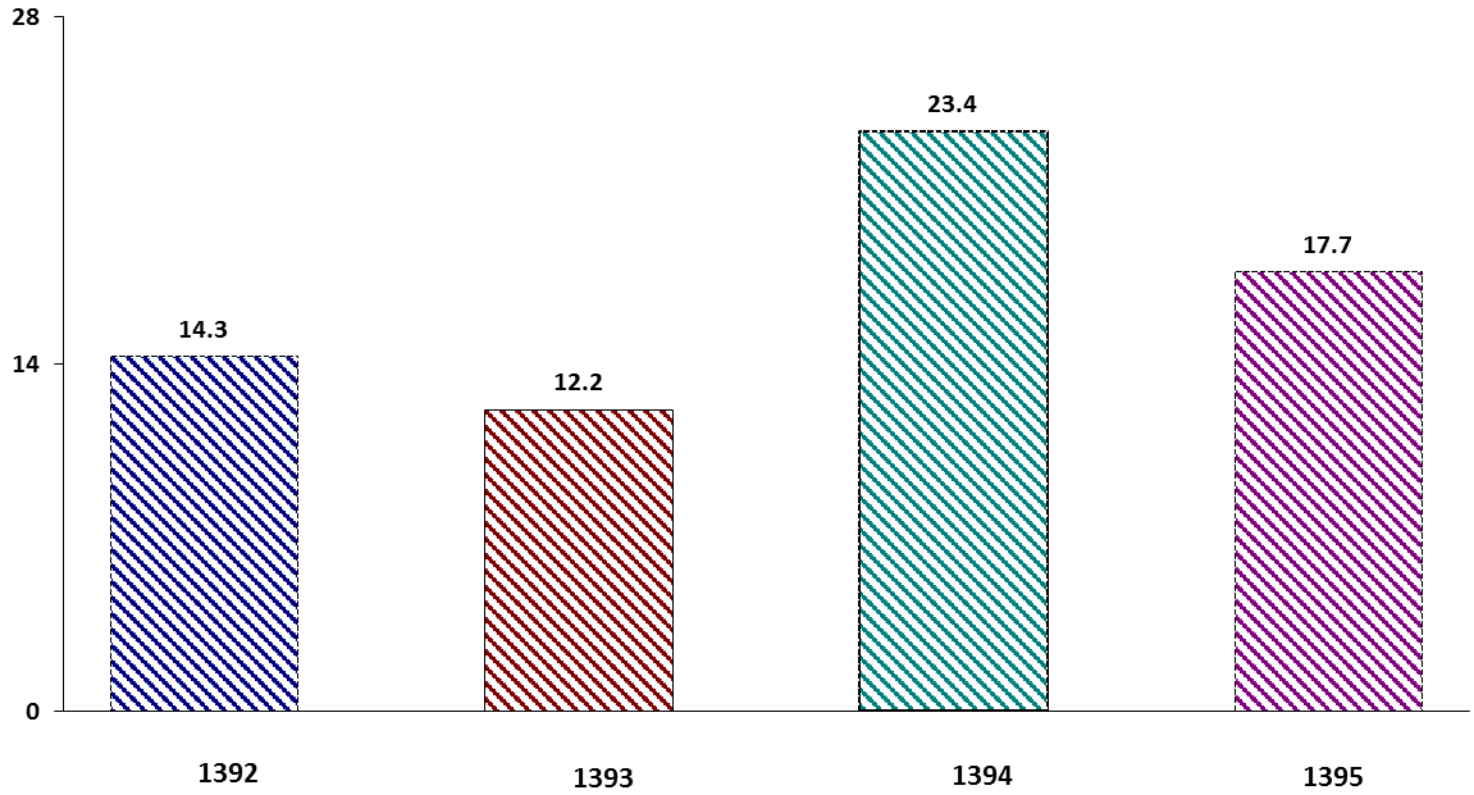
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در سیستان و بلوچستان(95-1392)



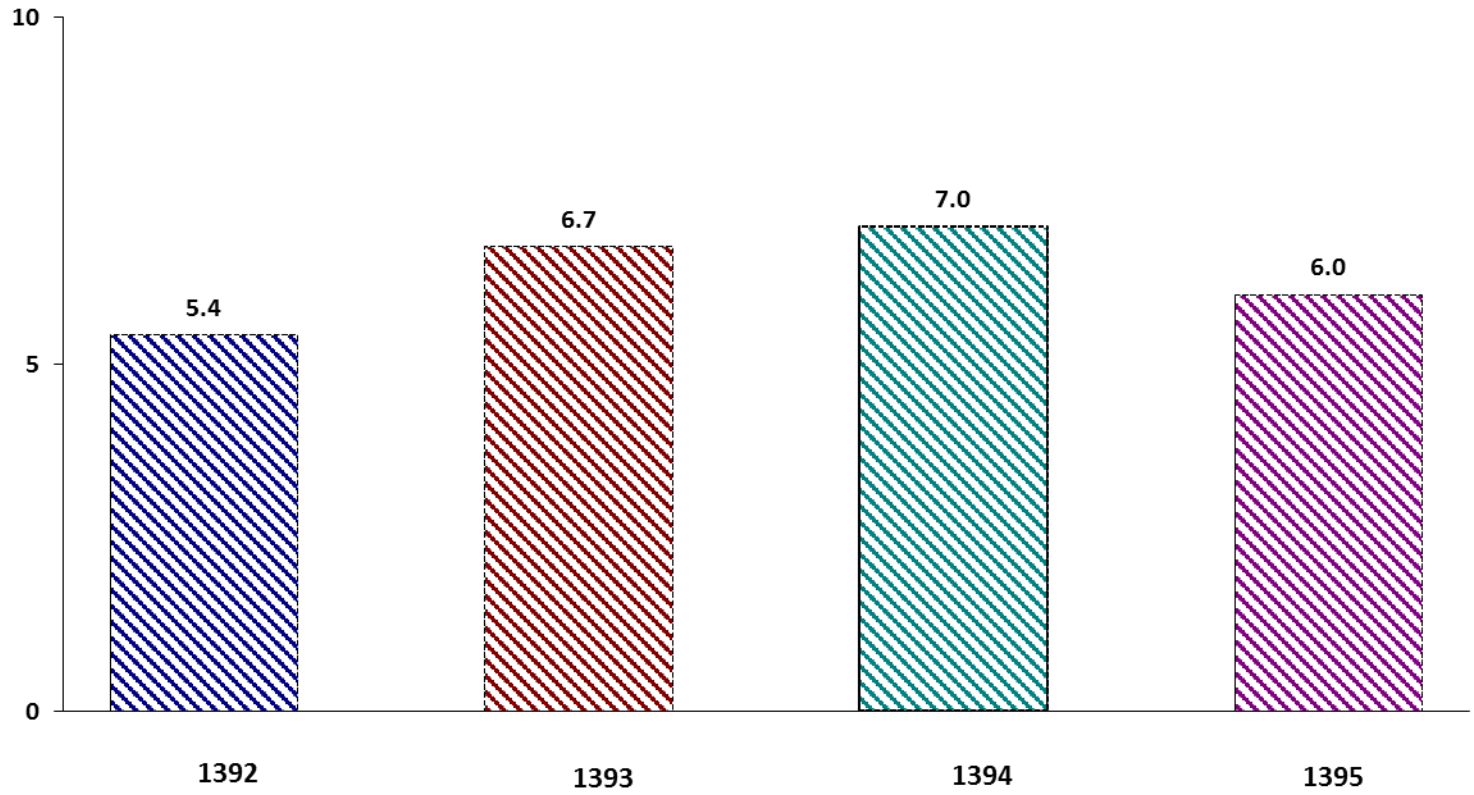
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در سیستان و بلوچستان(95-1392)



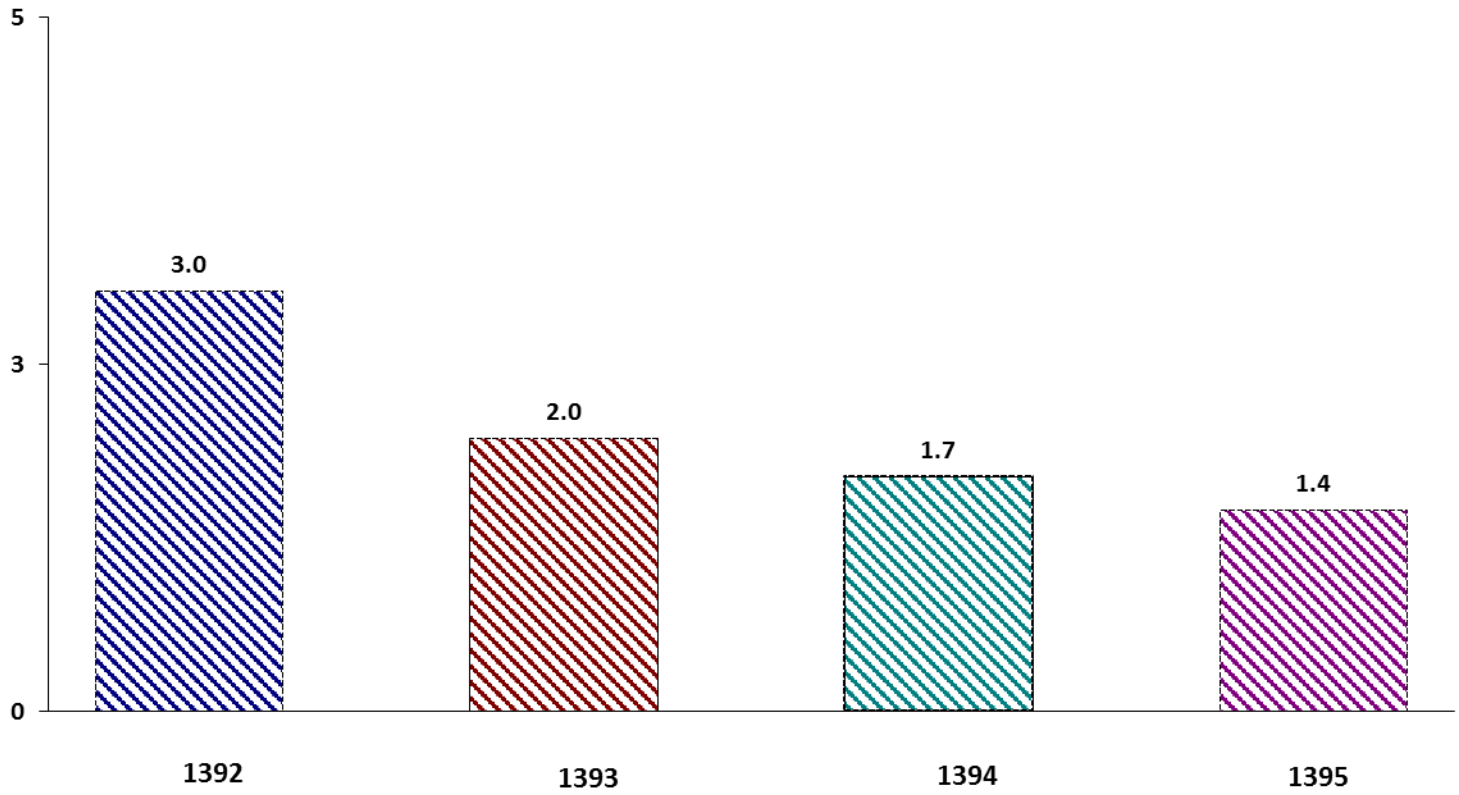
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در سیستان و بلوچستان(95-1392)



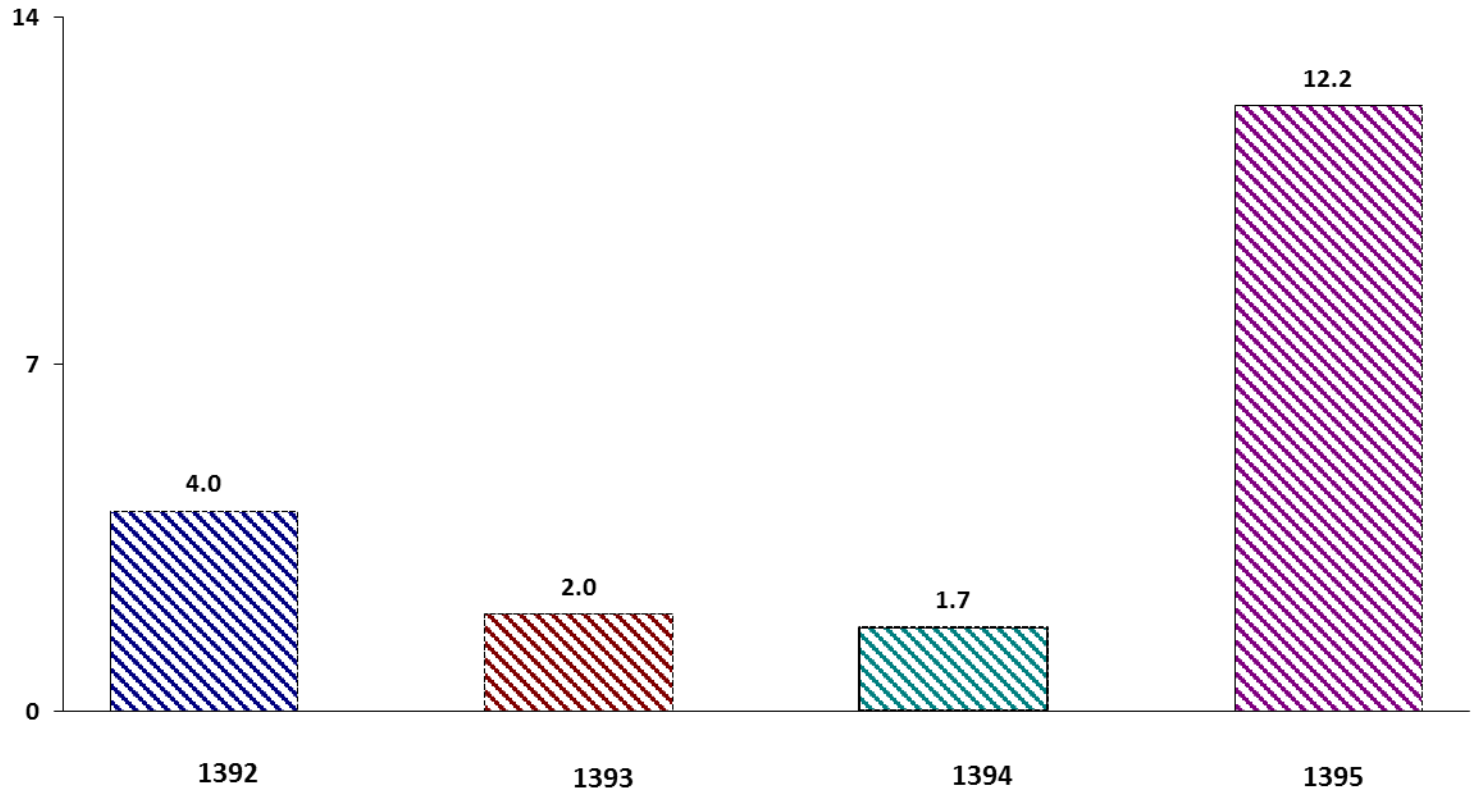
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در فارس(95-1392)



شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در فارس(95-1392)



شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در فارس(95-1392)



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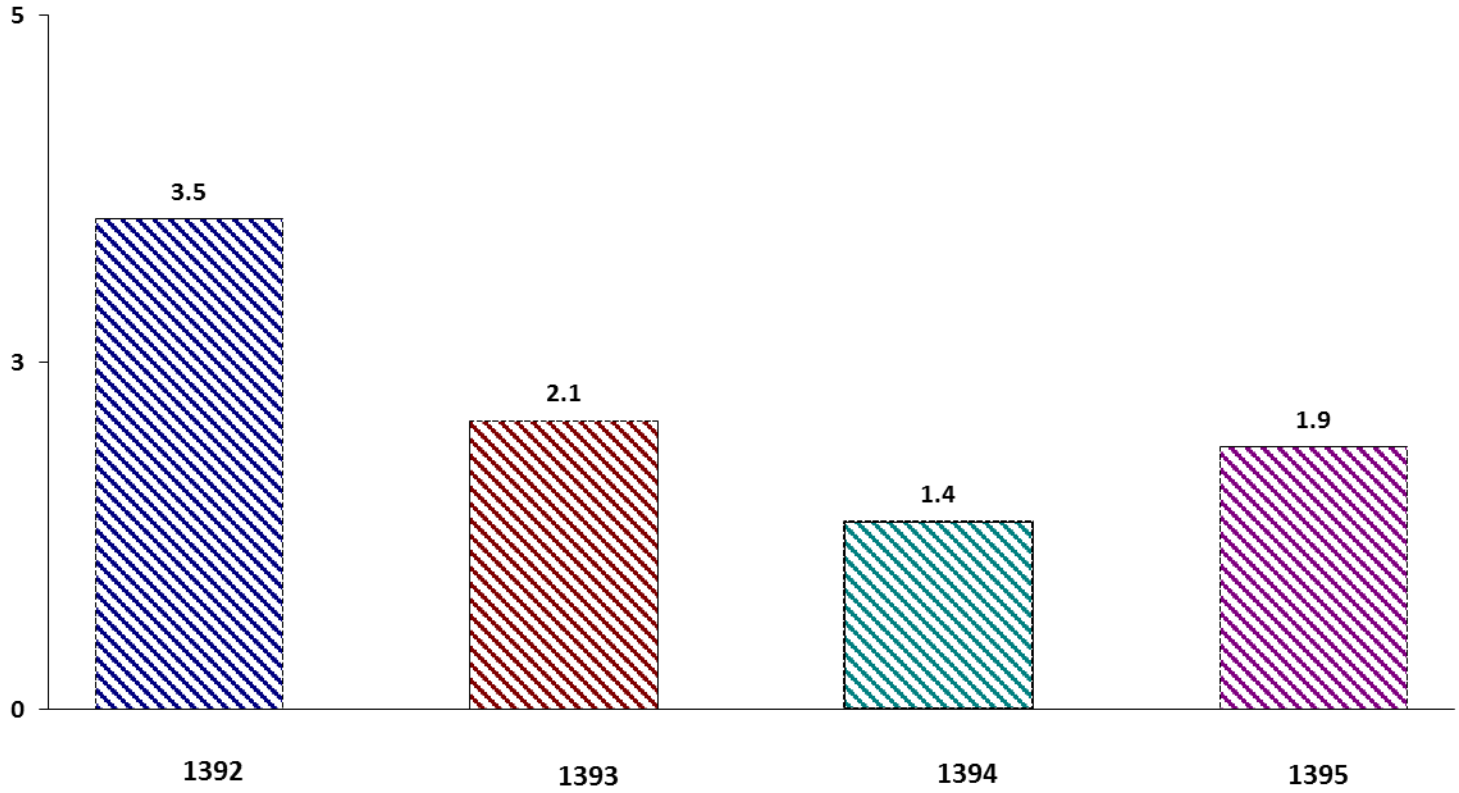

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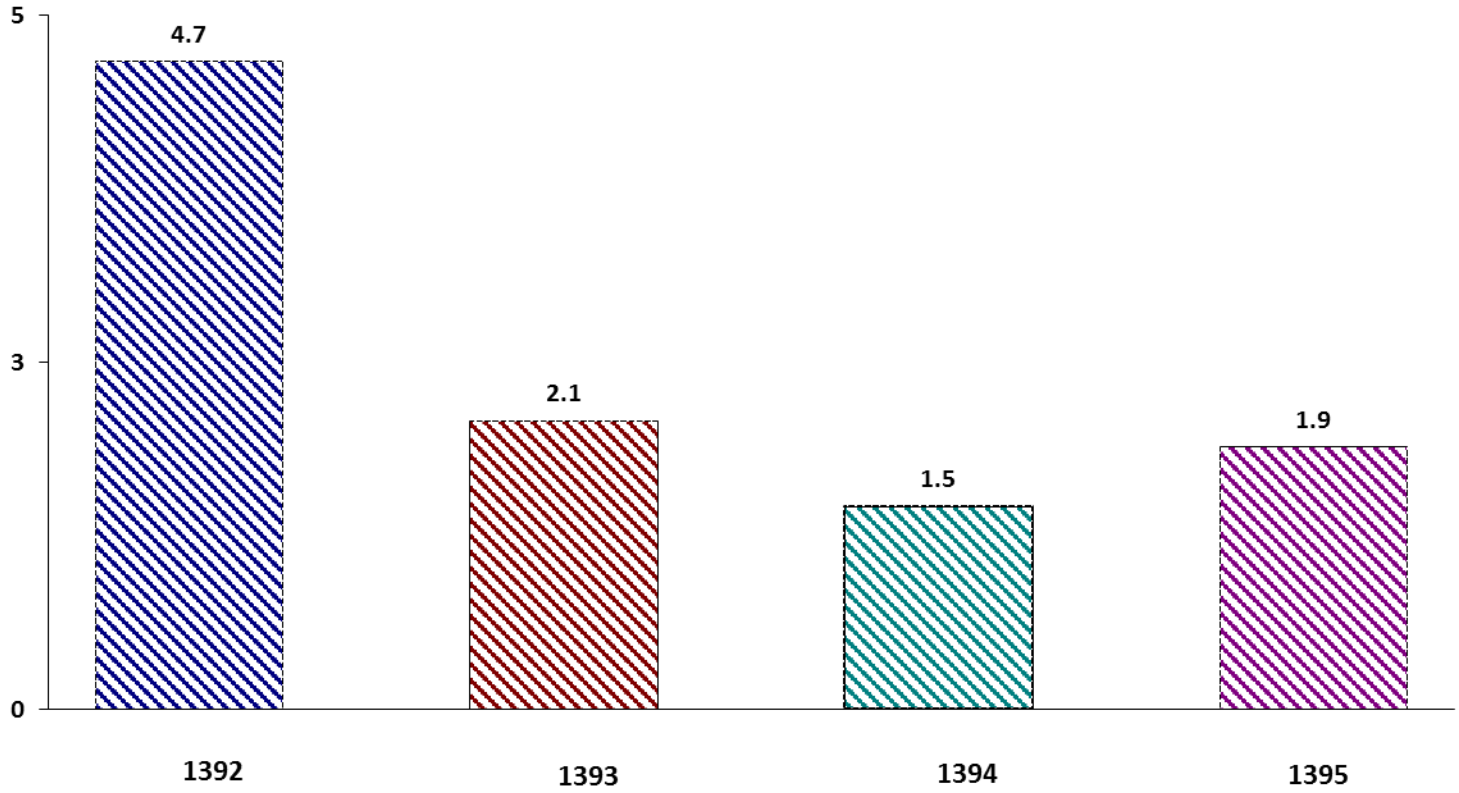
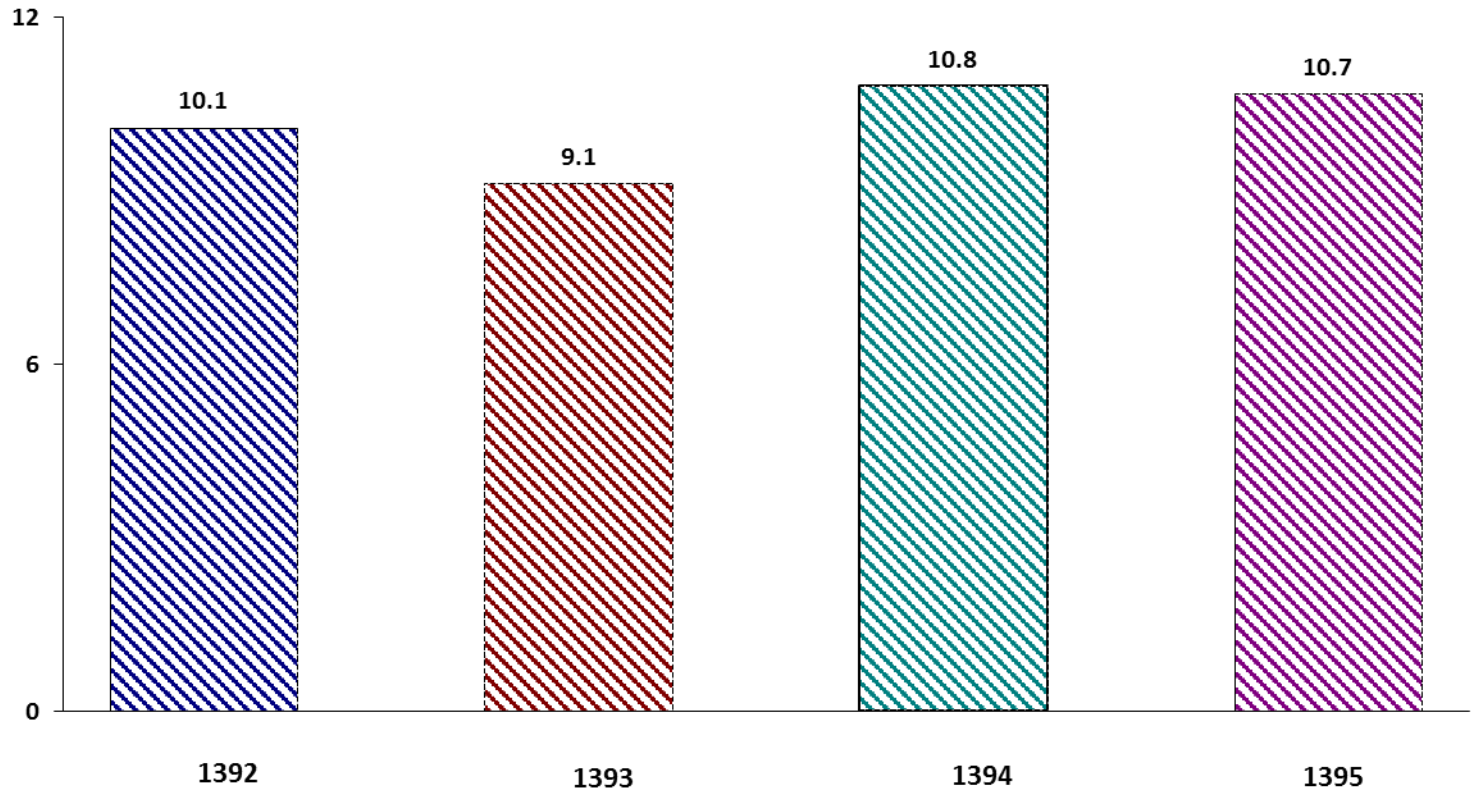
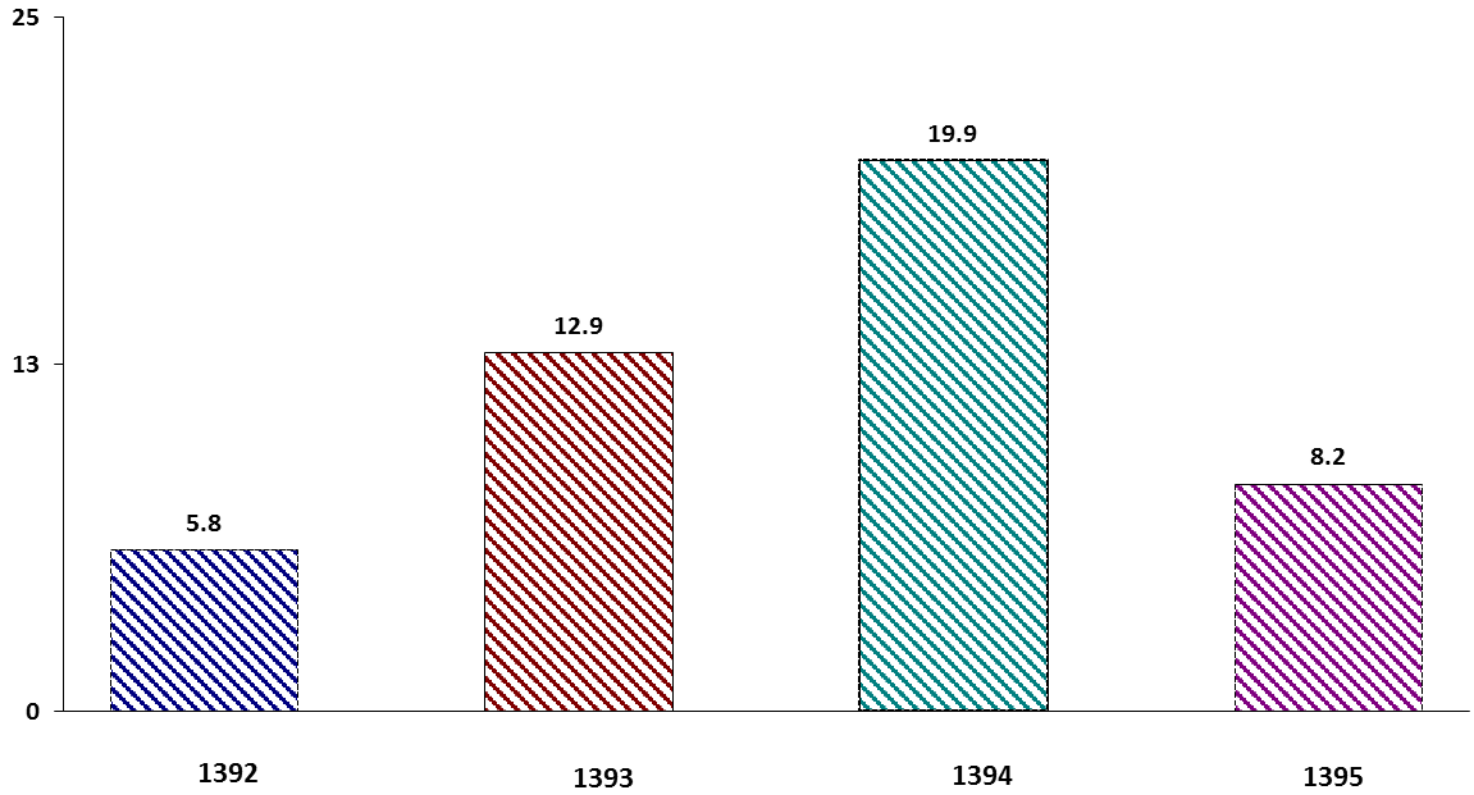


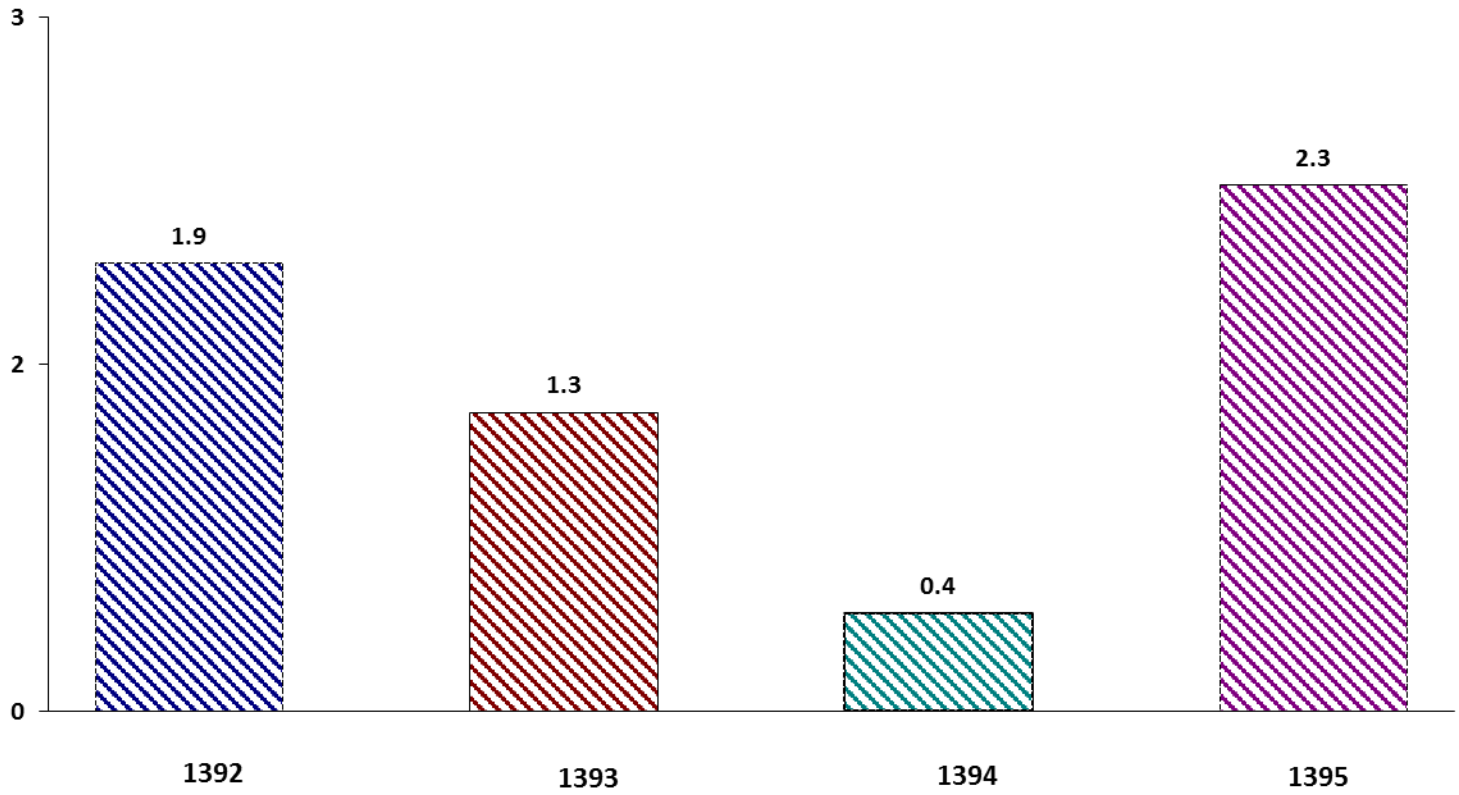
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در فارس(95-1392)



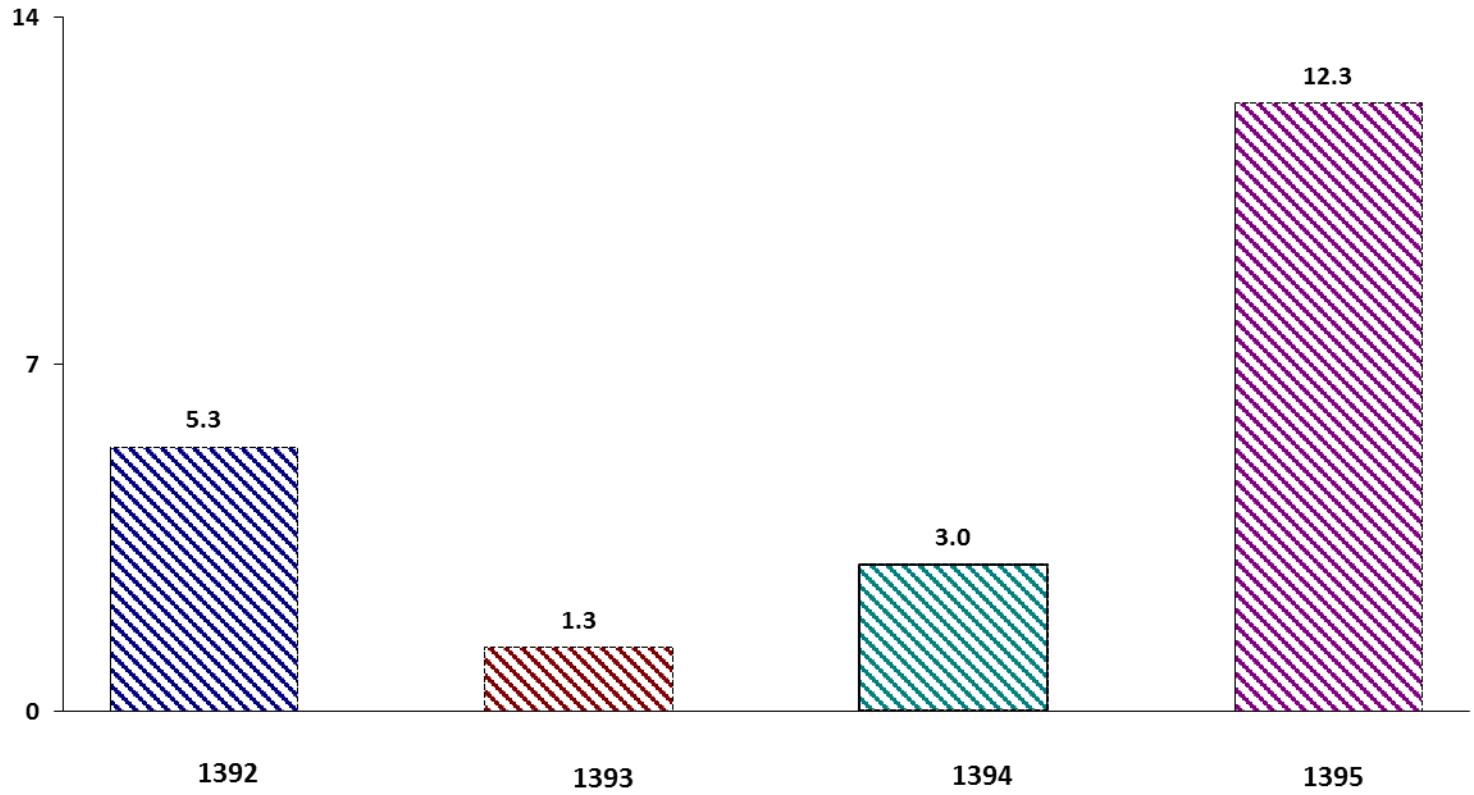
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در قزوین(95-1392)



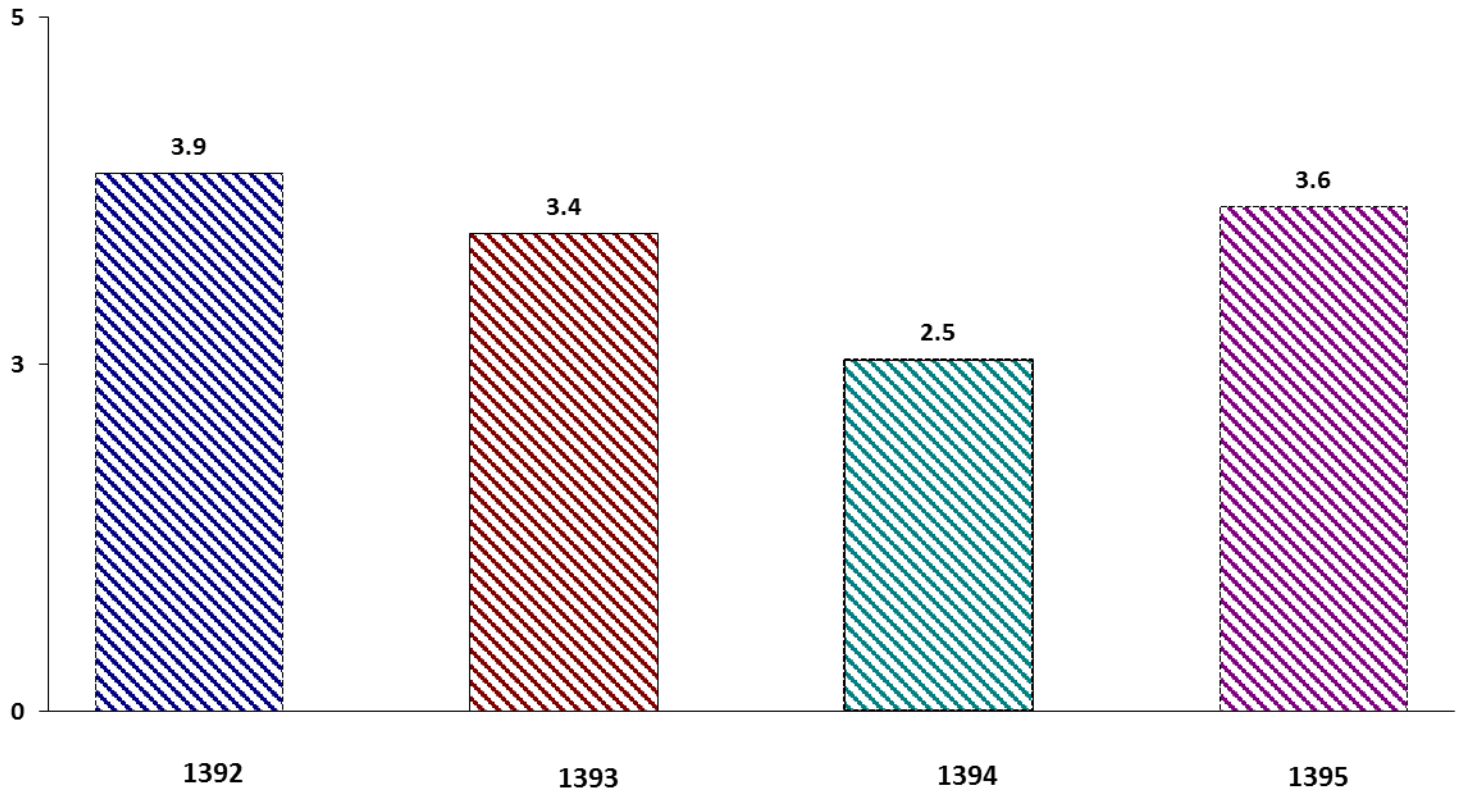
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در قزوین(95-1392)



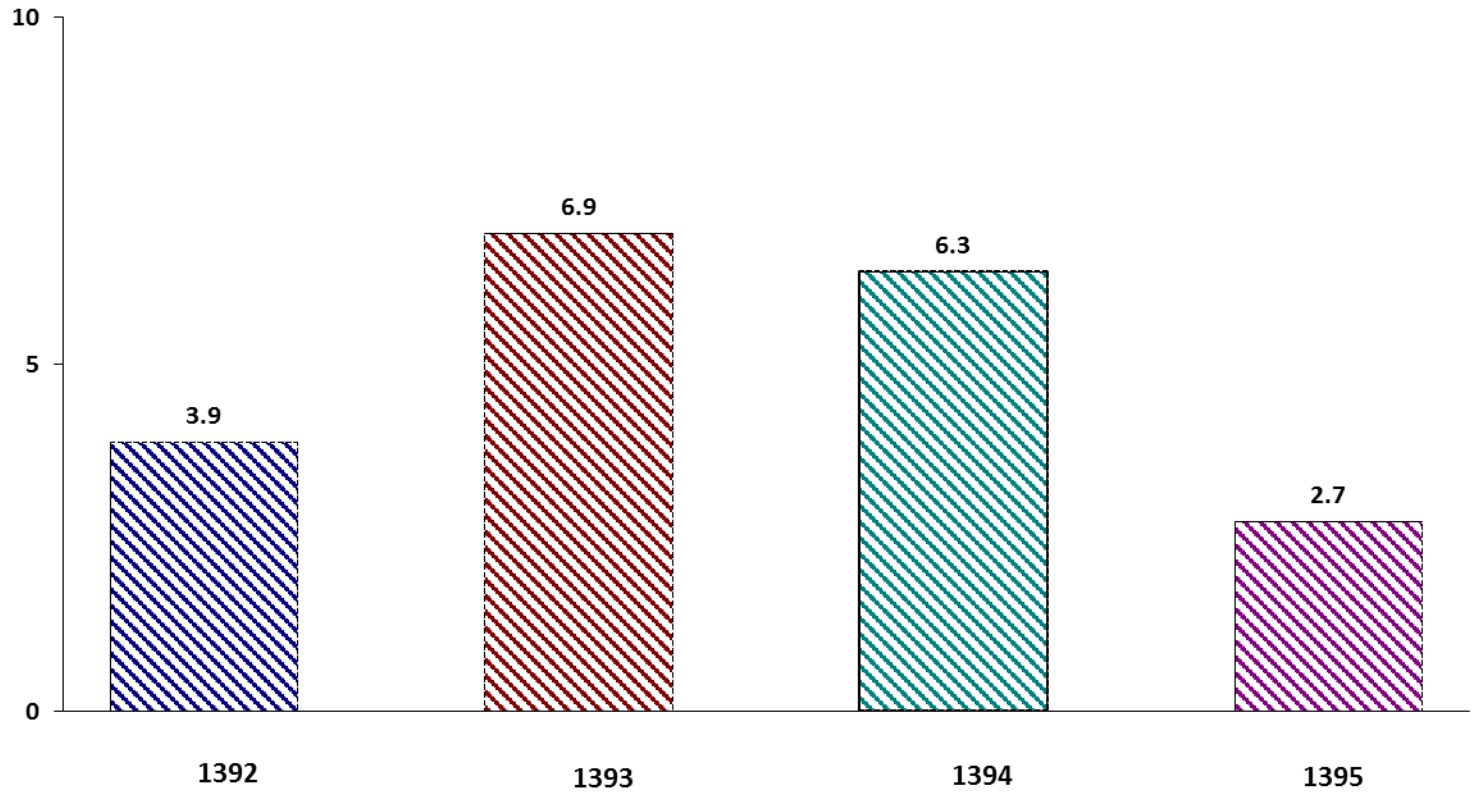
شیوع کلی ناهنجاری های مادرزادی عضلاتي و اسکلتي(در هر ده هزار تولد) در قزوین(95-1392)



شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) در قزوین(95-1392)



شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در قزوین(95-1392)



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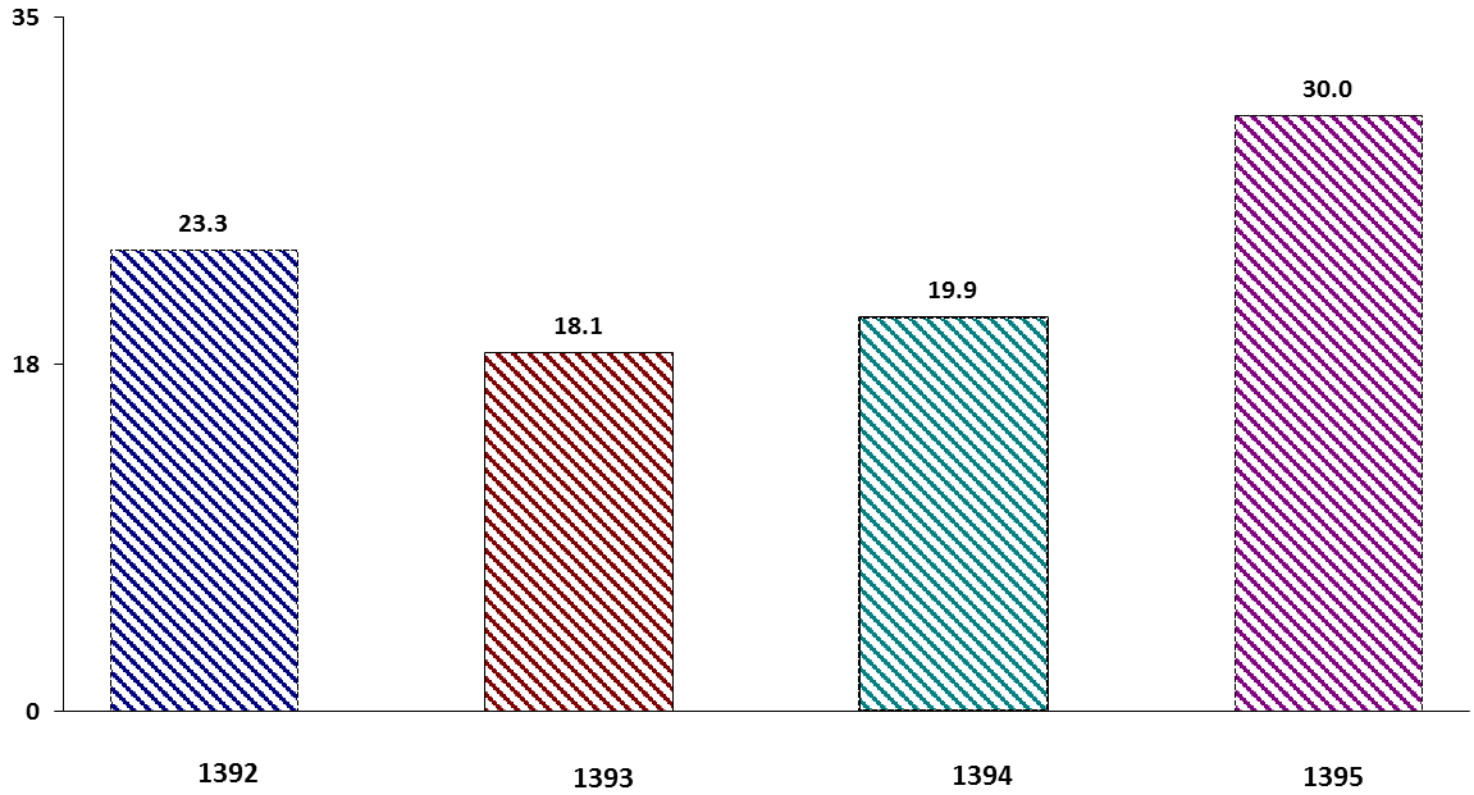
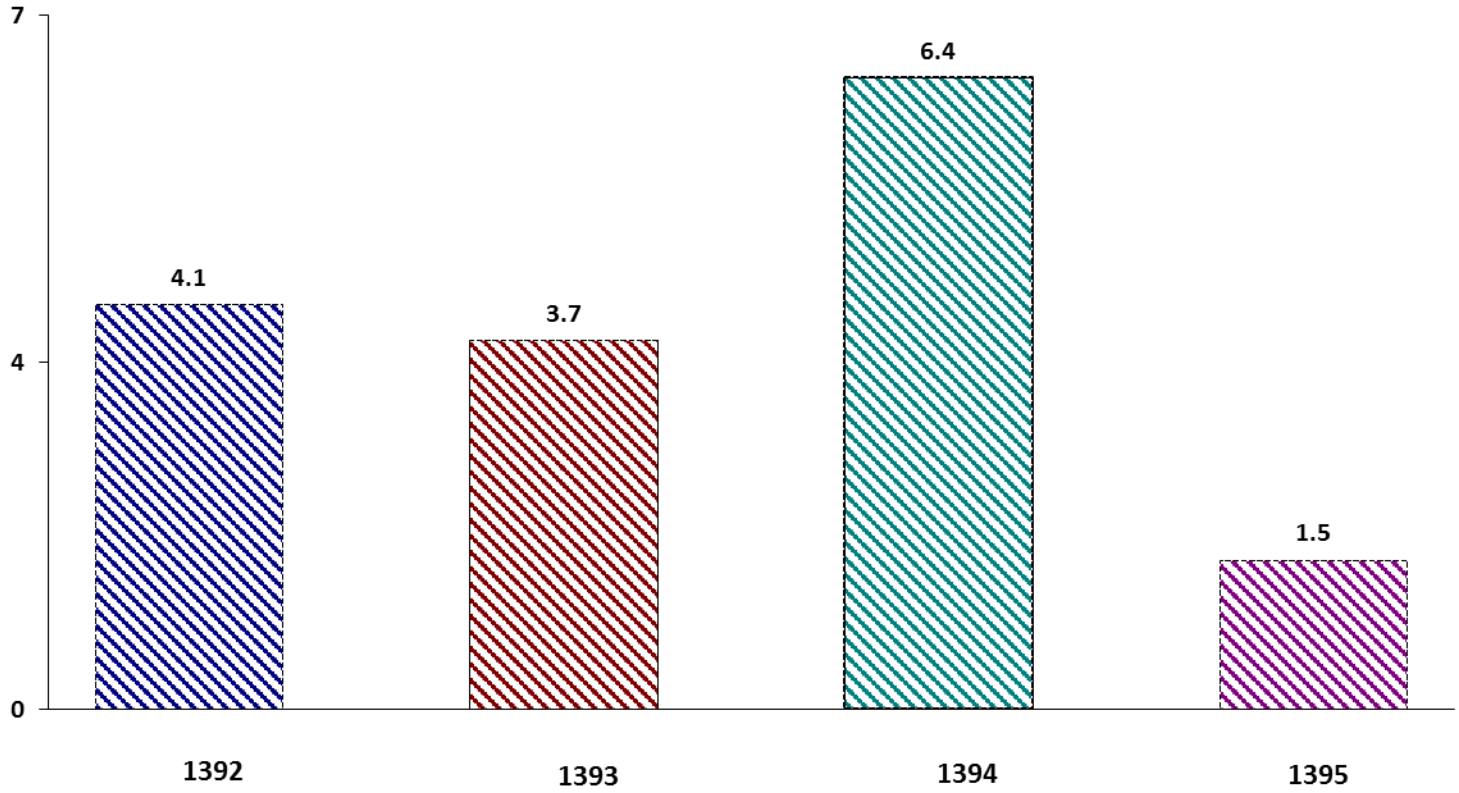
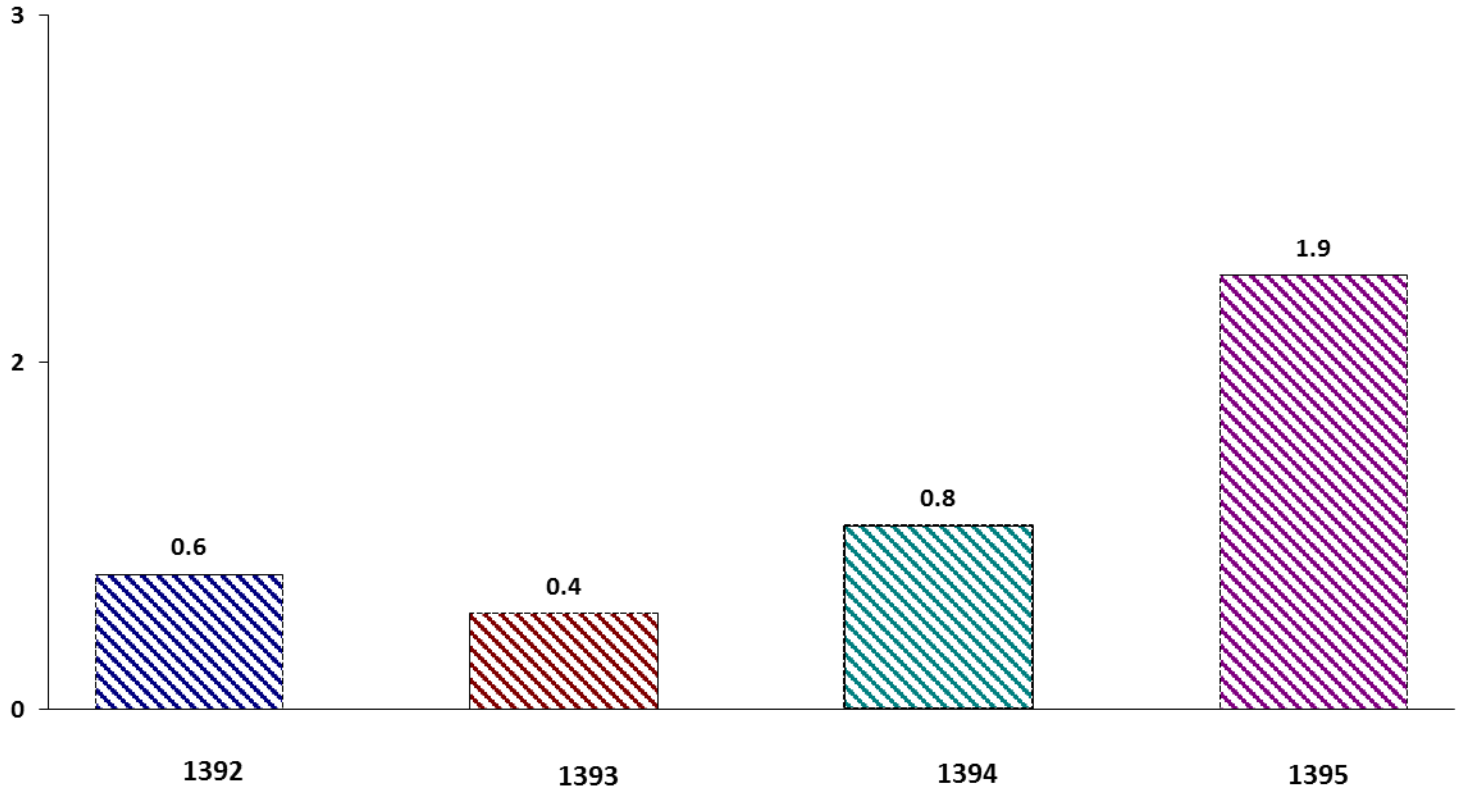


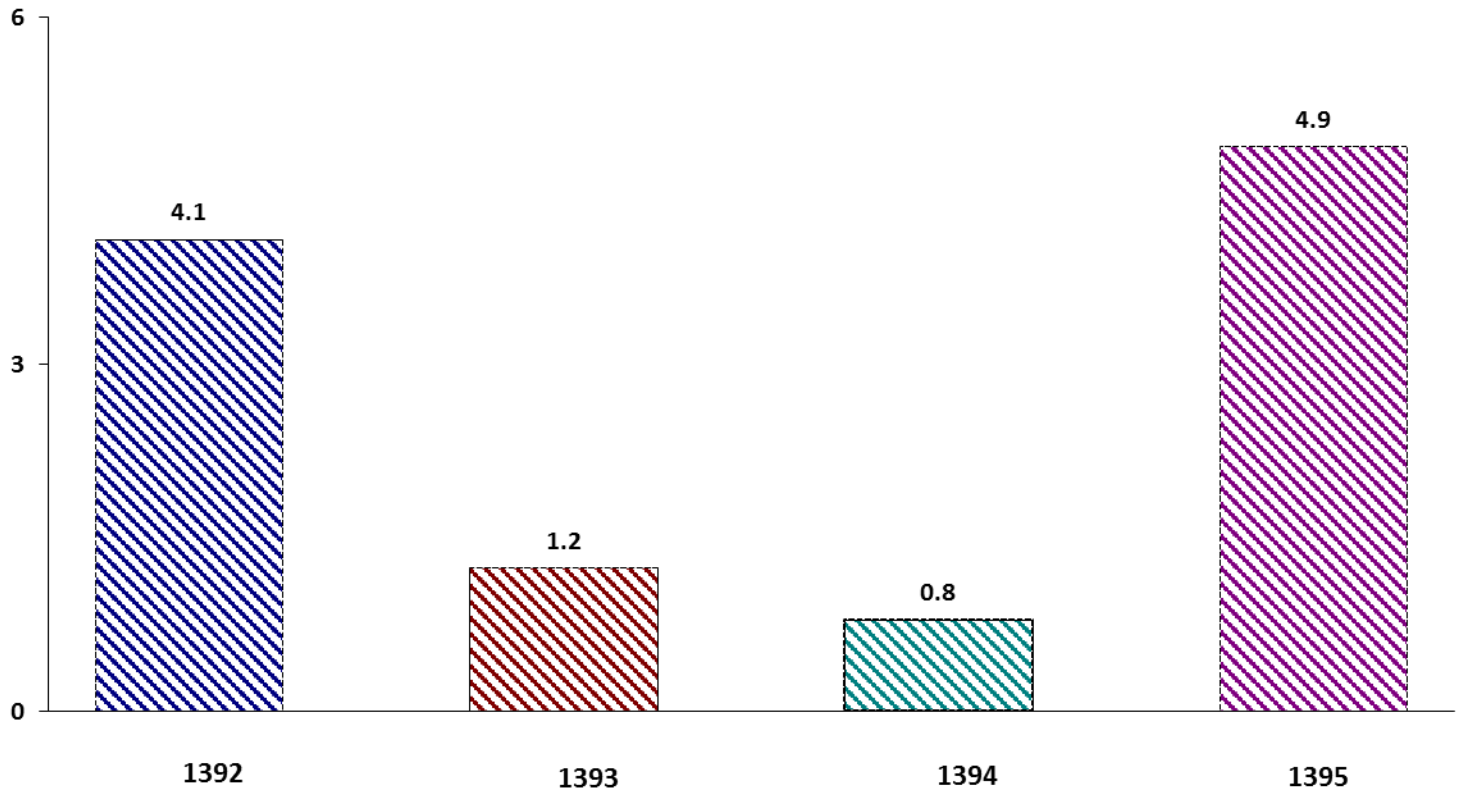
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) در قم(95-1392)



شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) در قم(95-1392)



شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) در قم(95-1392)



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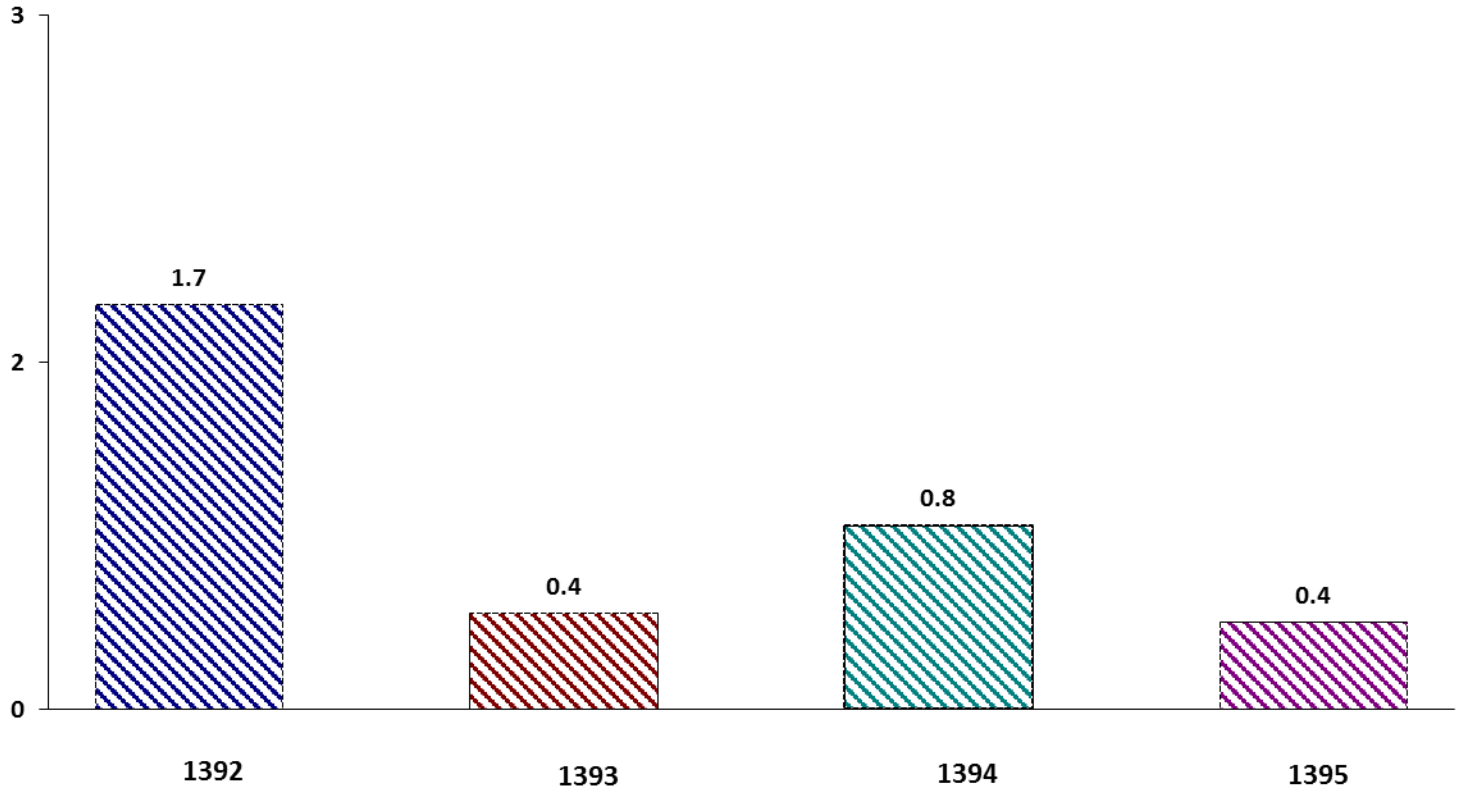
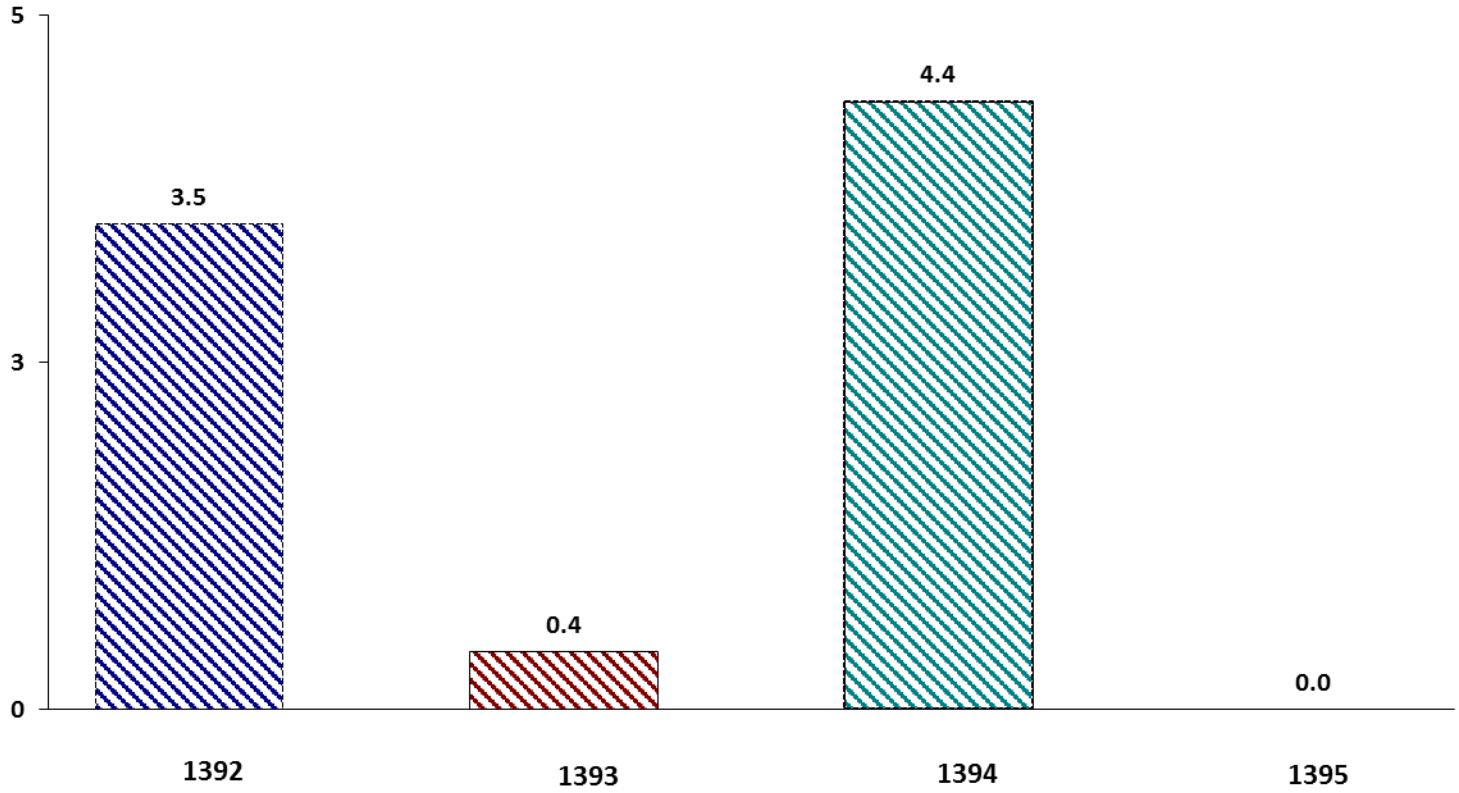
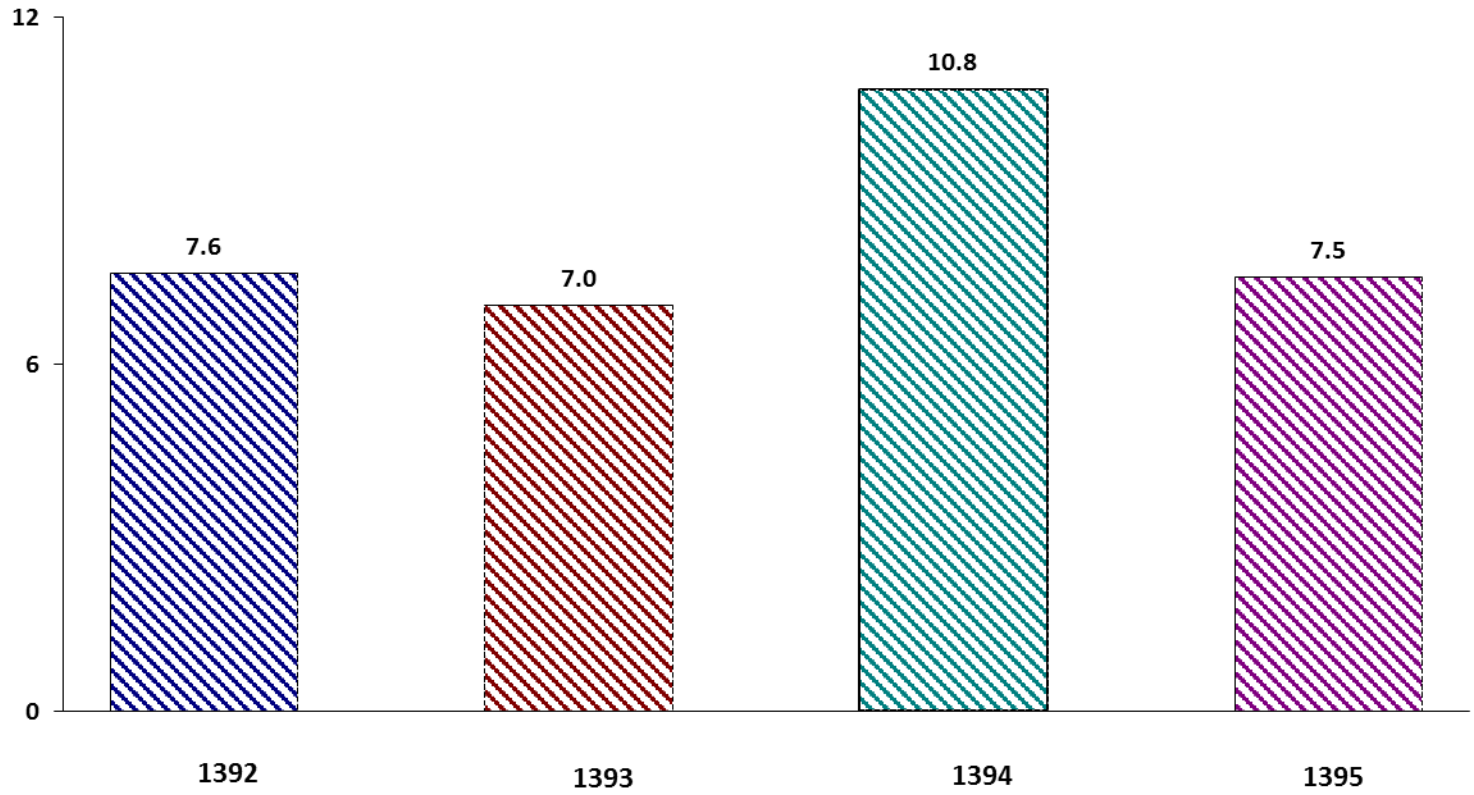


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) در قم(95-1392)



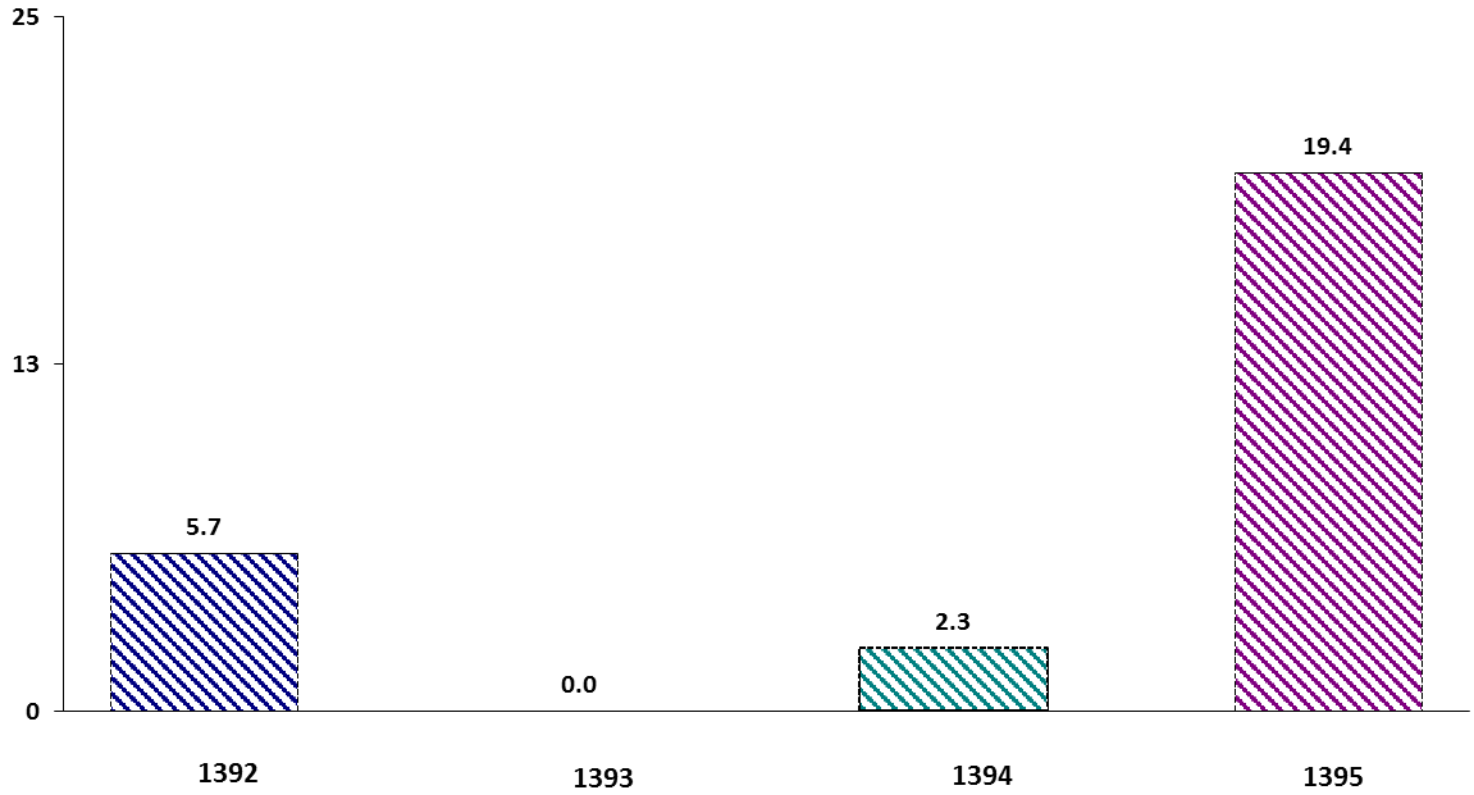
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) در قم(95-1392)



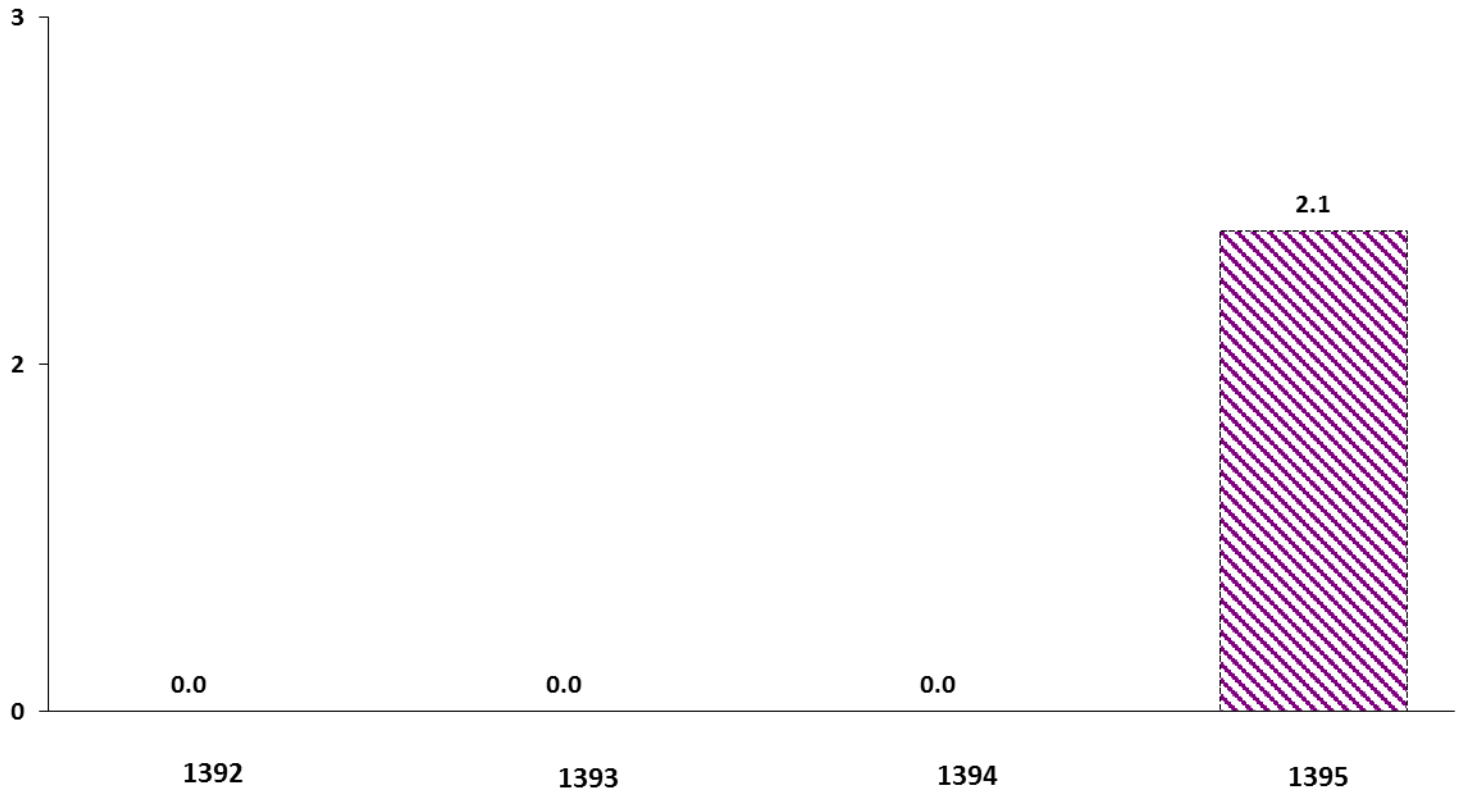
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درکهکیلویه و بویر احمد(95-1392)

شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درکهکیلویه و بویر احمد(95-1392)

شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درکهکیلویه و بویر احمد(95-1392)

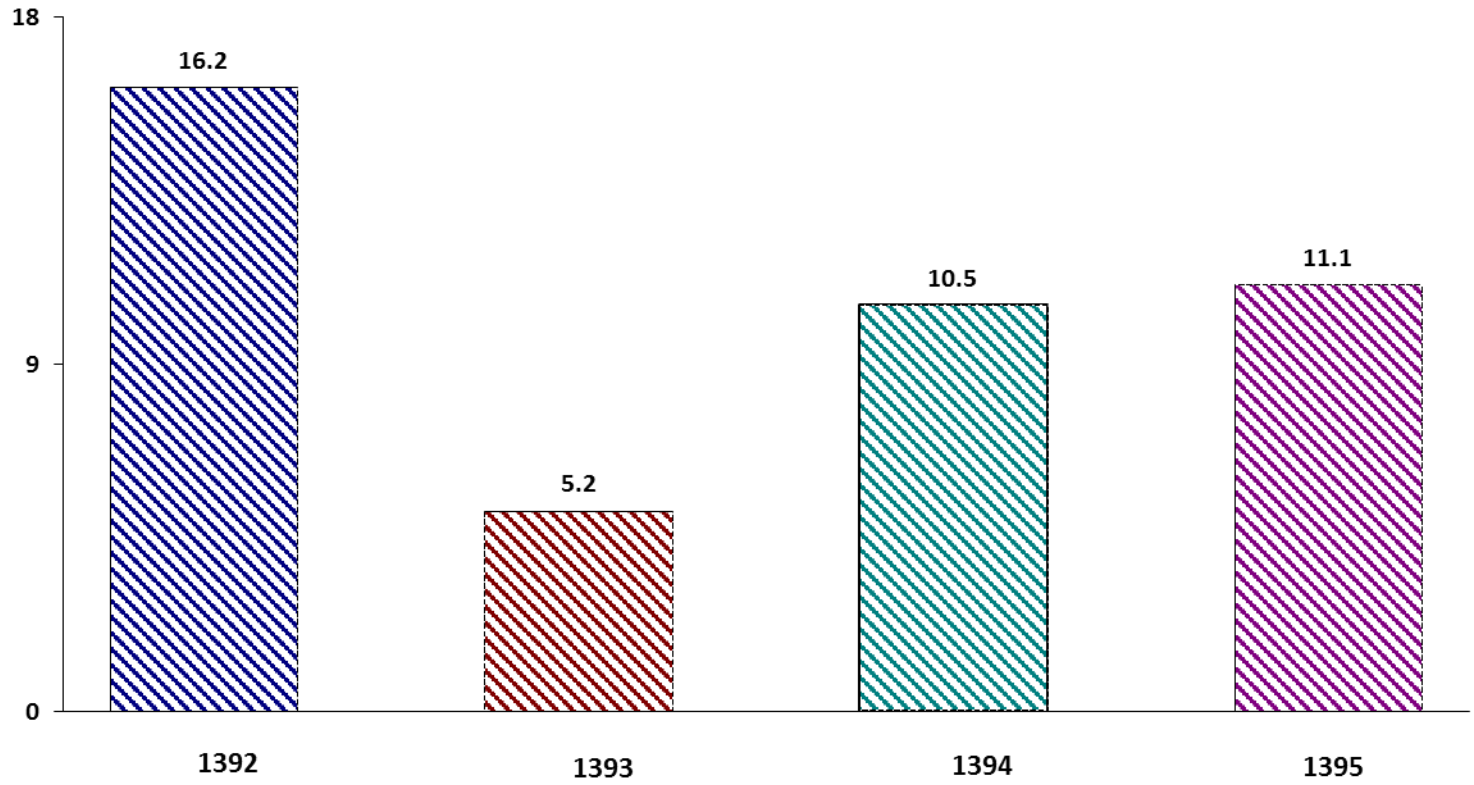


شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درکهکیلویه و بویر احمد(95-1392)

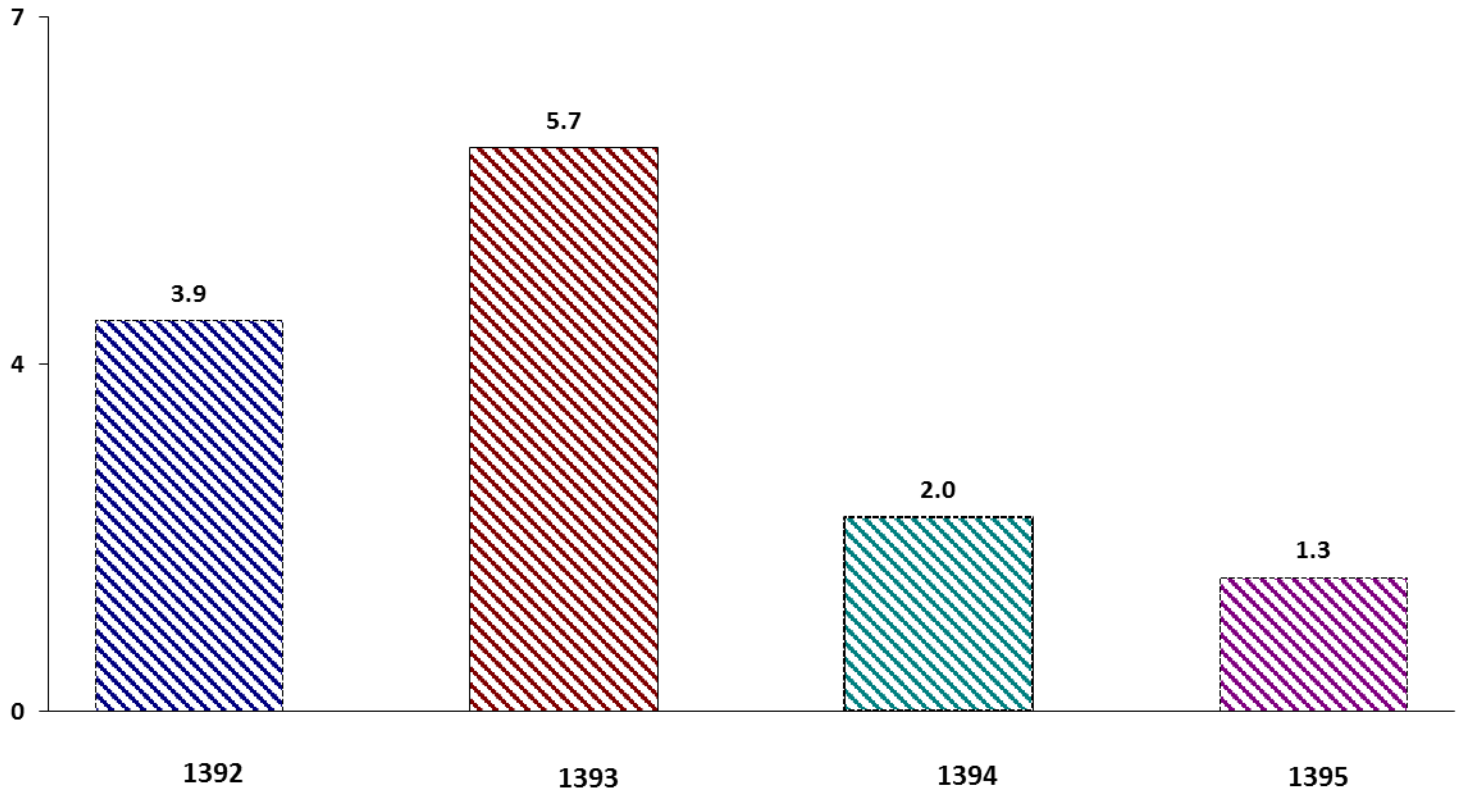


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درکهکیلویه و بویر احمد(95-1392)

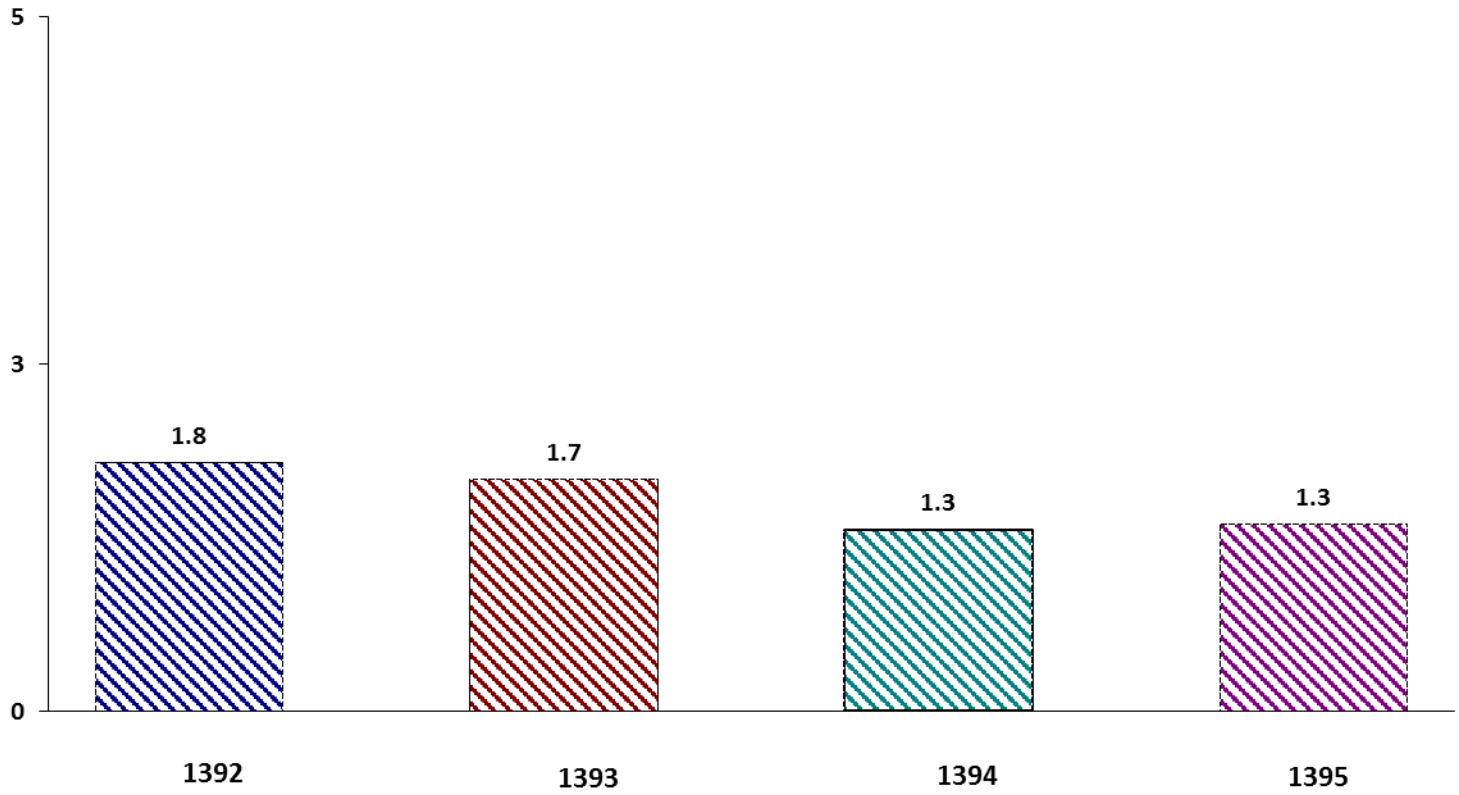
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درکهکیلویه و بویر احمد(95-1392)



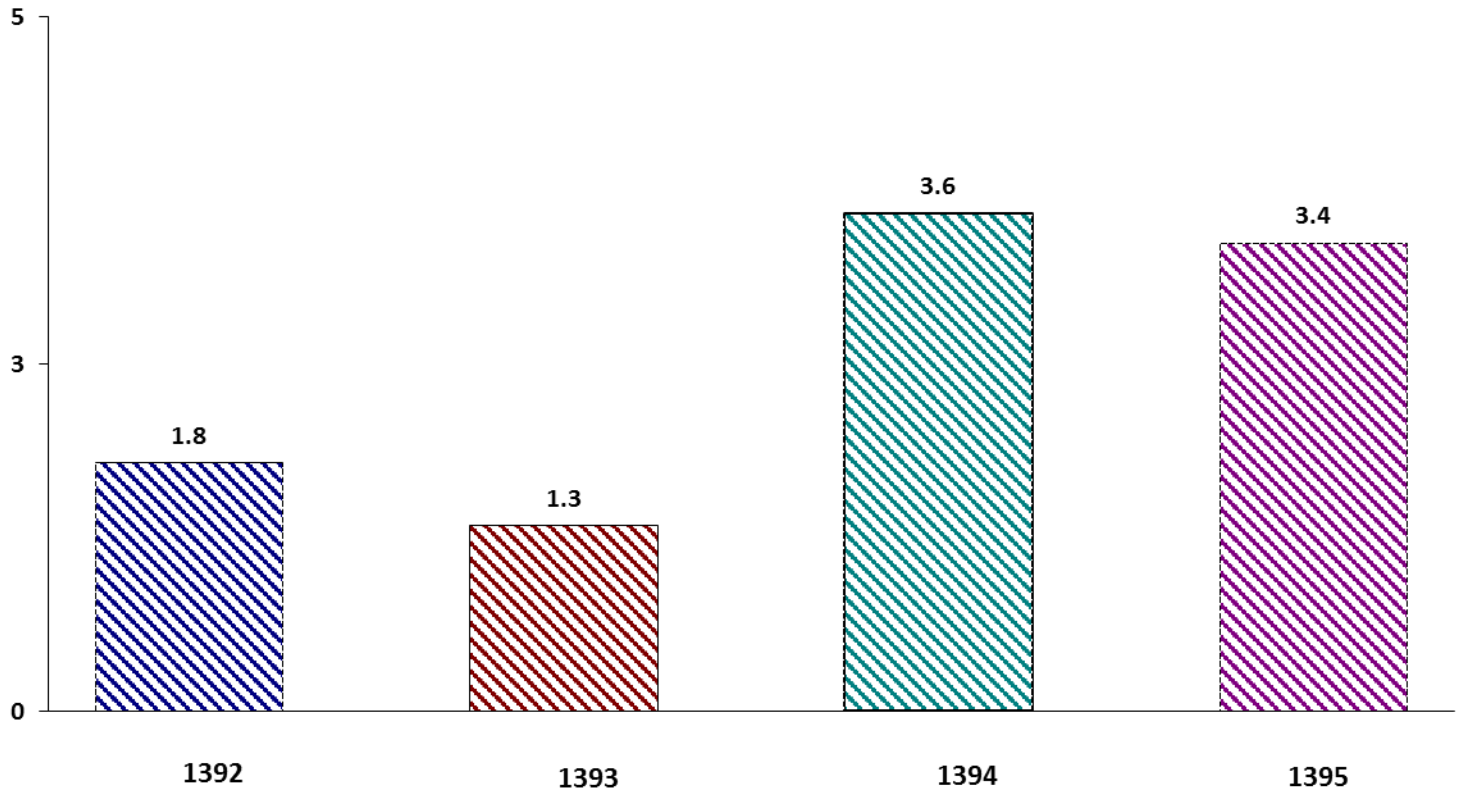
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درکردستان(95-1392)



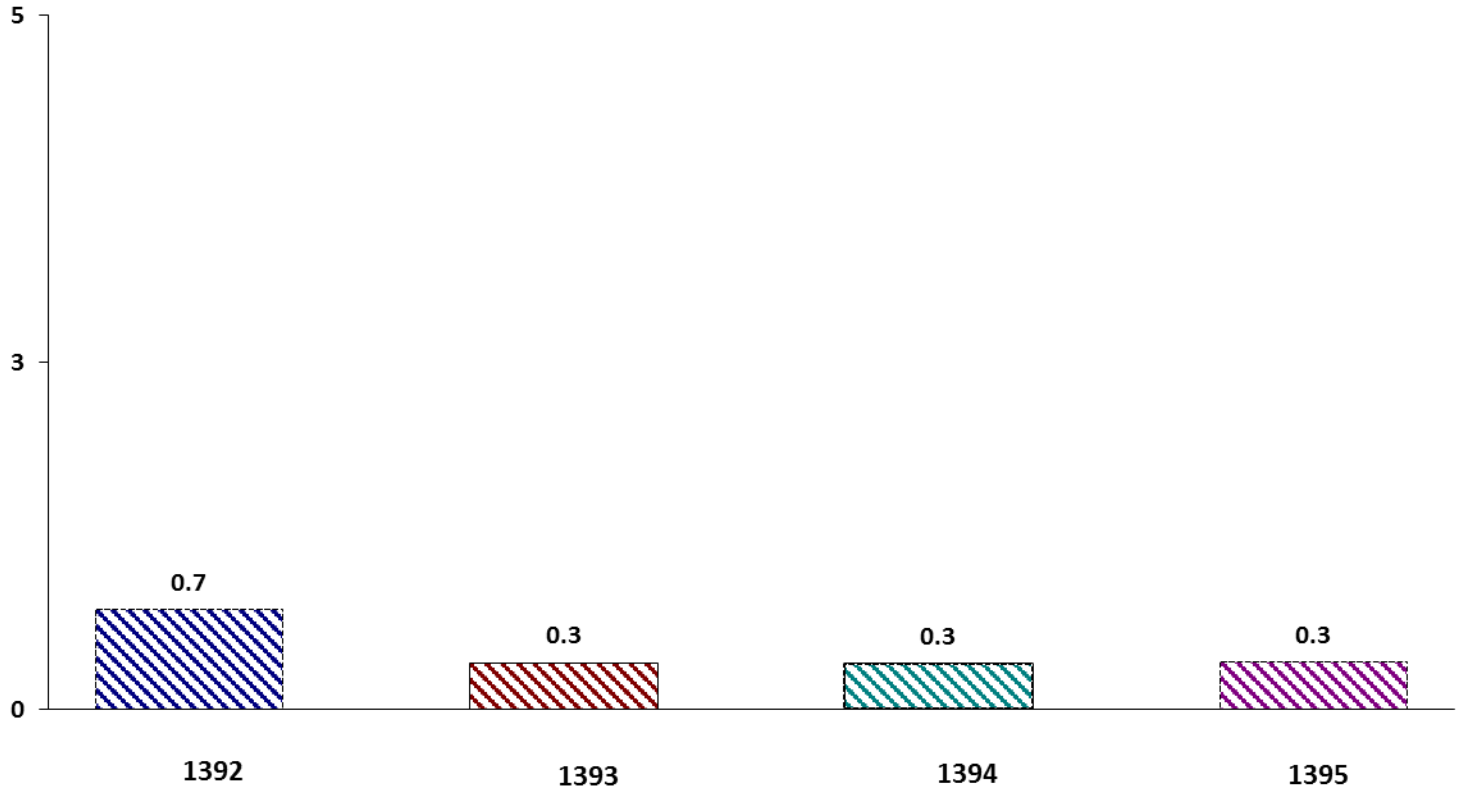
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درکردستان(95-1392)



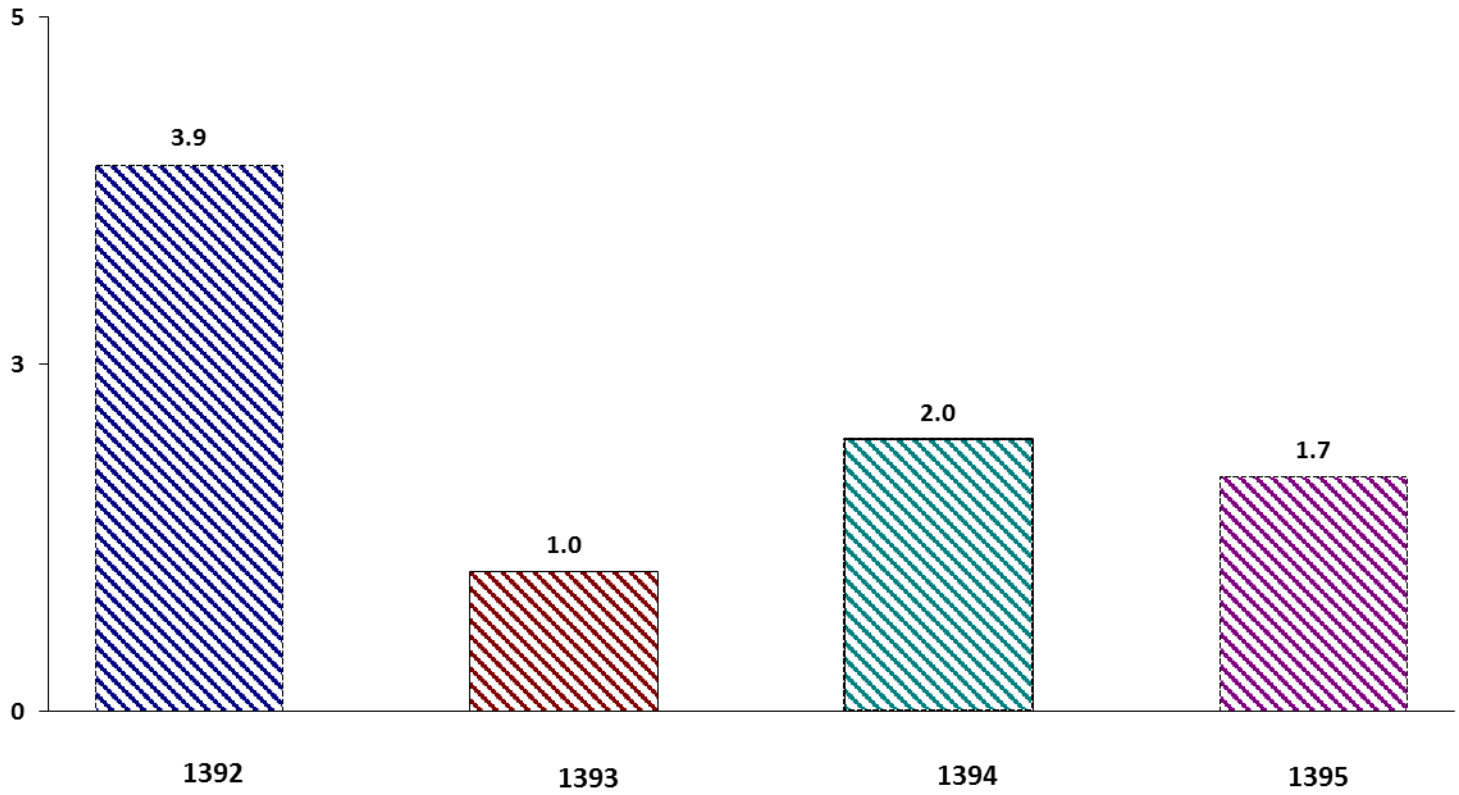
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درکردستان(95-1392)



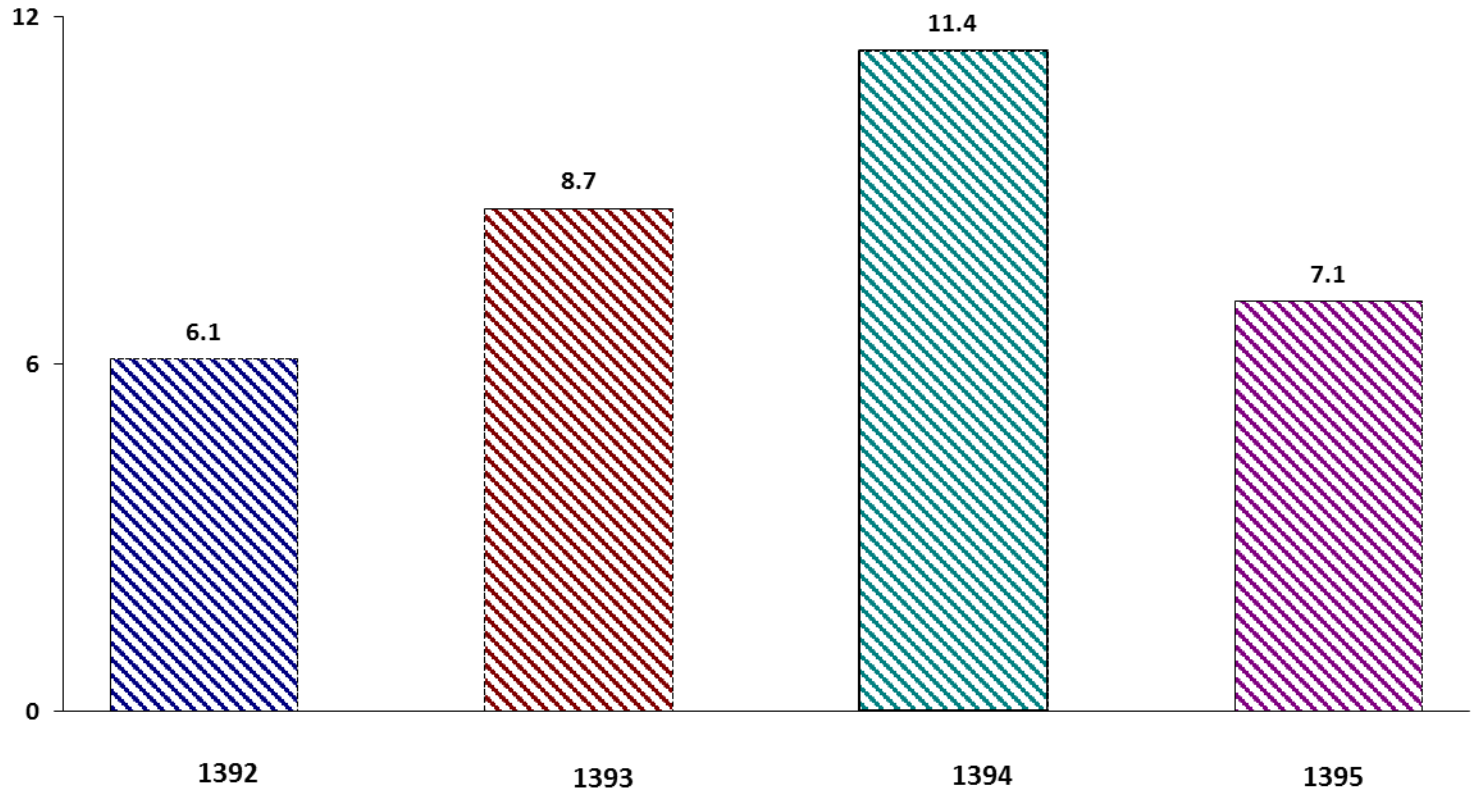
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درکردستان(95-1392)



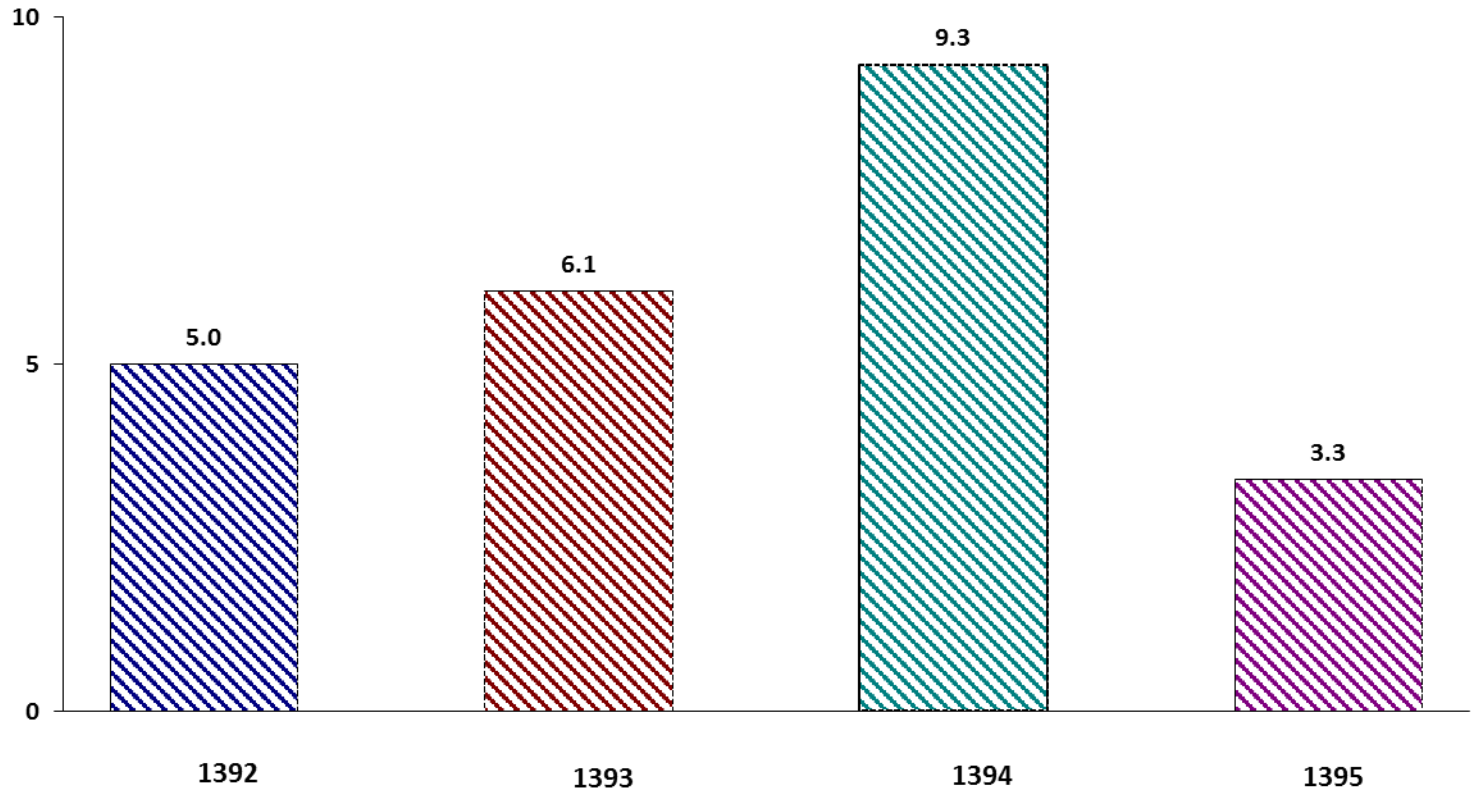
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درکردستان(95-1392)



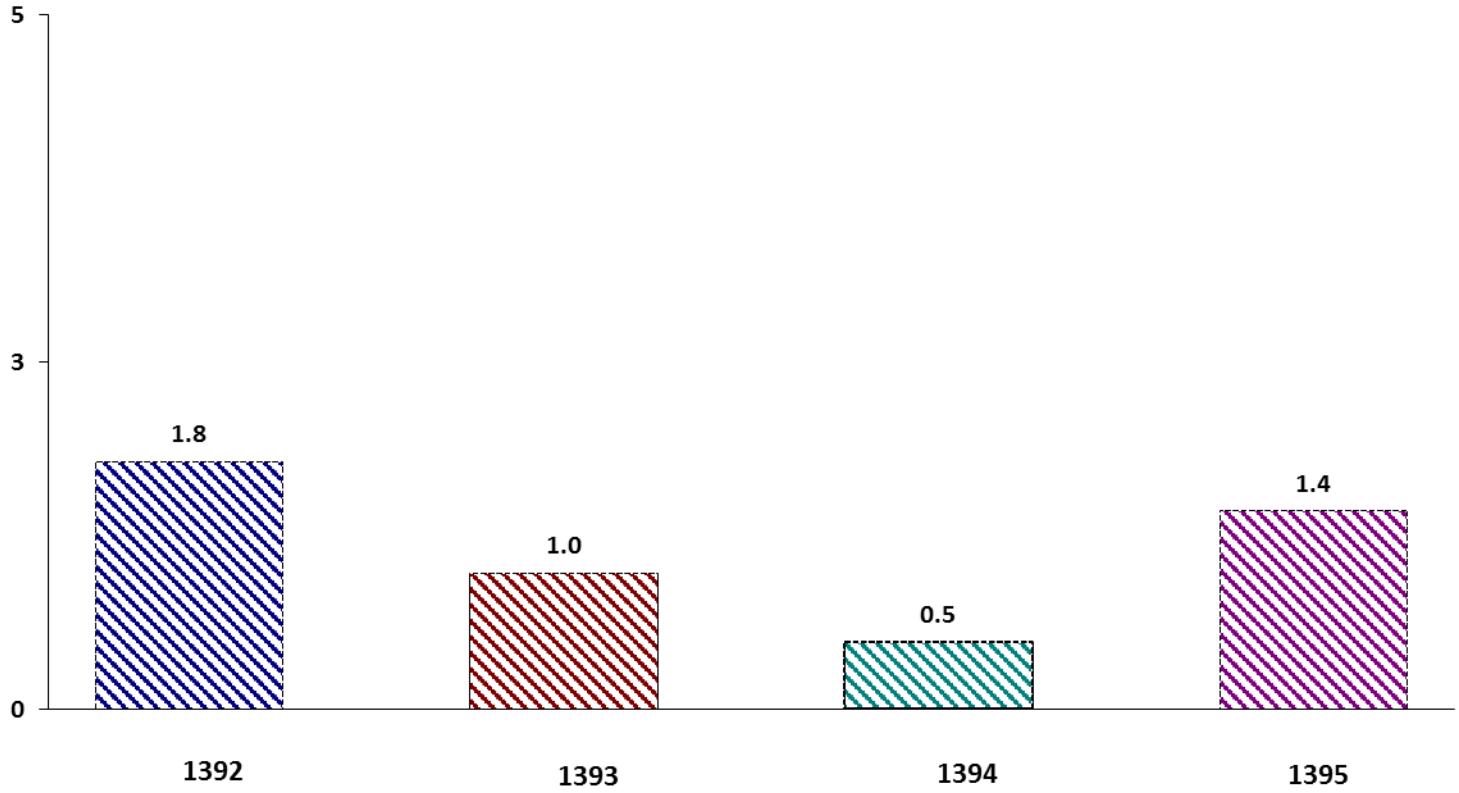
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درکردستان(95-1392)



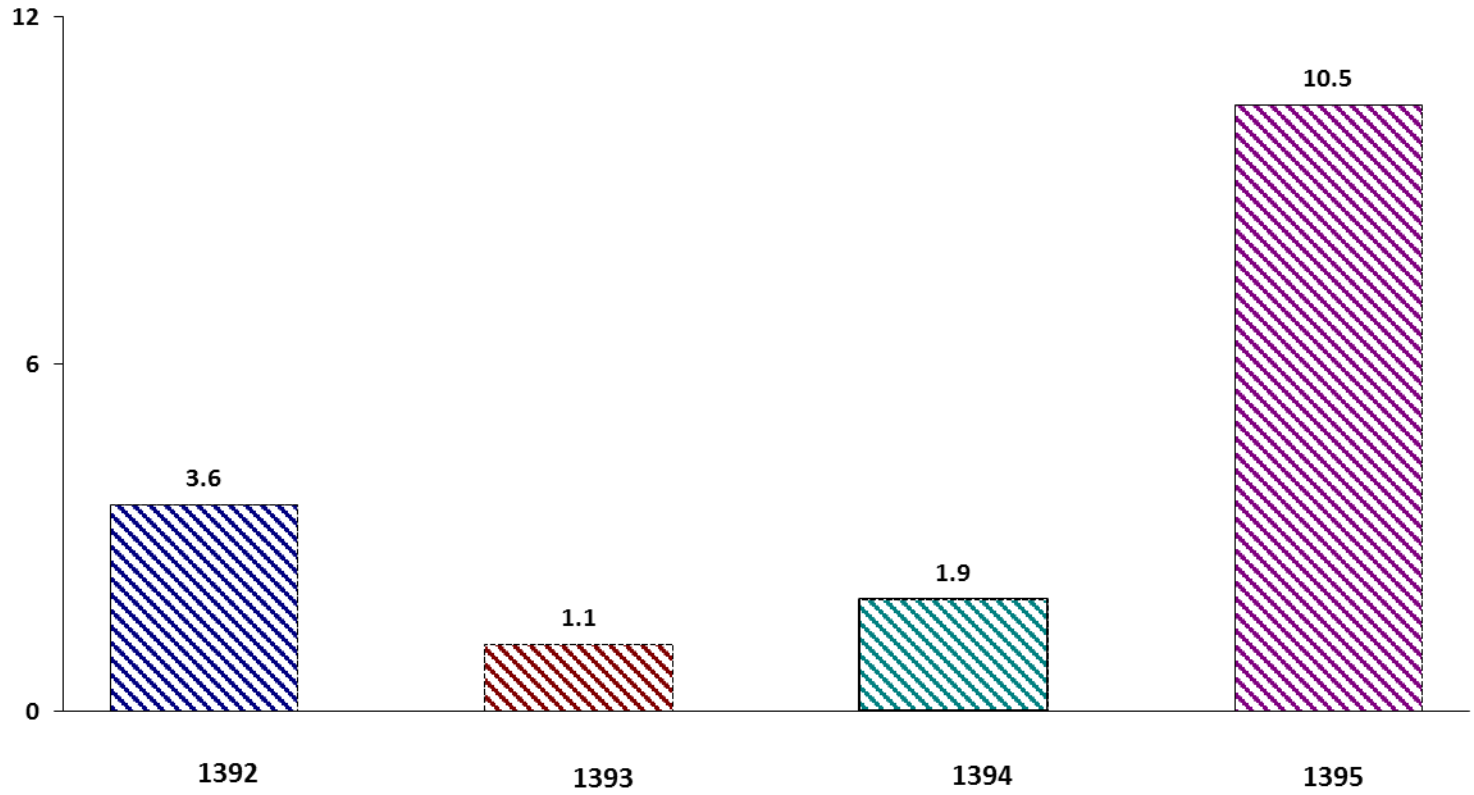
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درکرمان(95-1392)



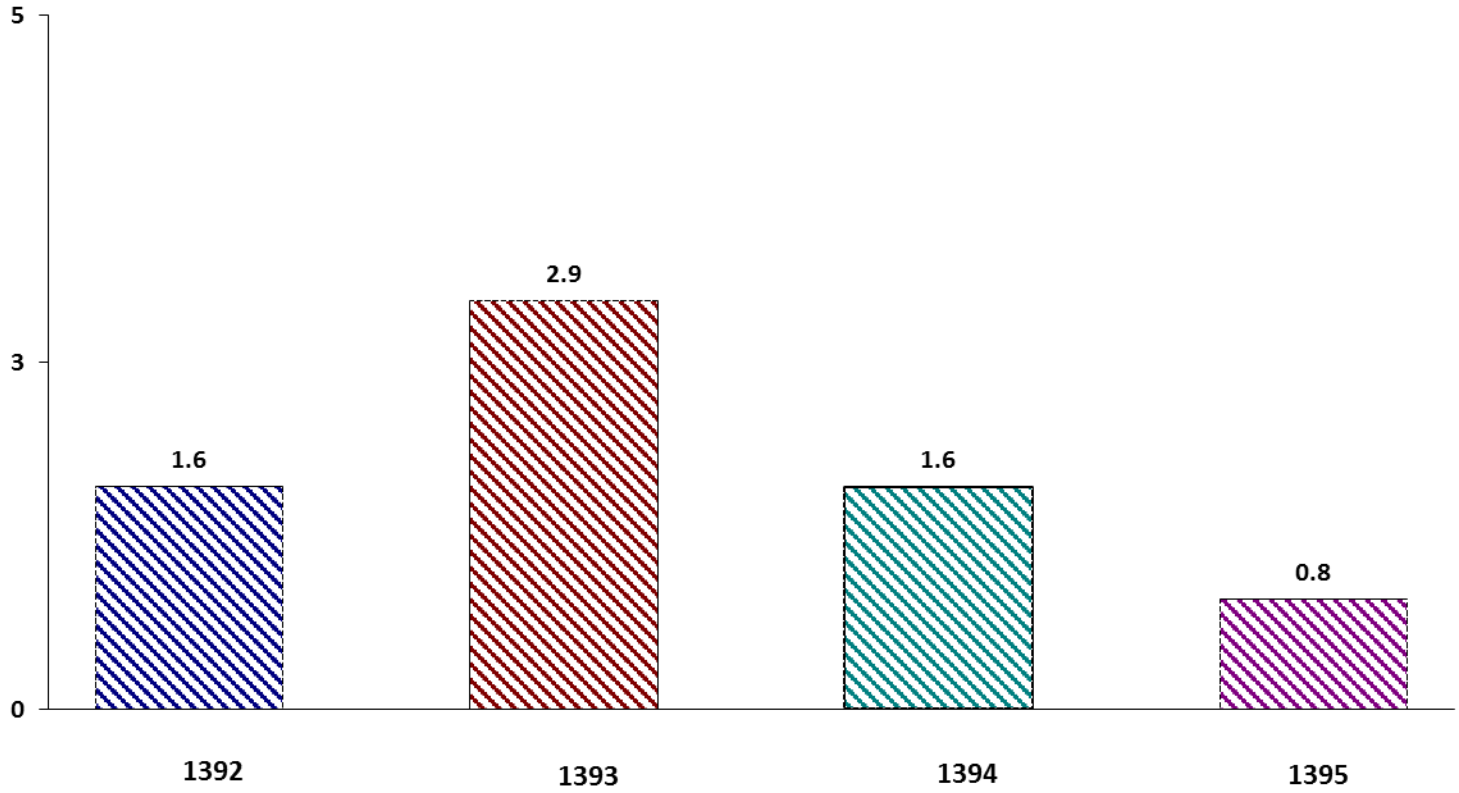
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درکرمان(95-1392)



شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درکرمان(95-1392)

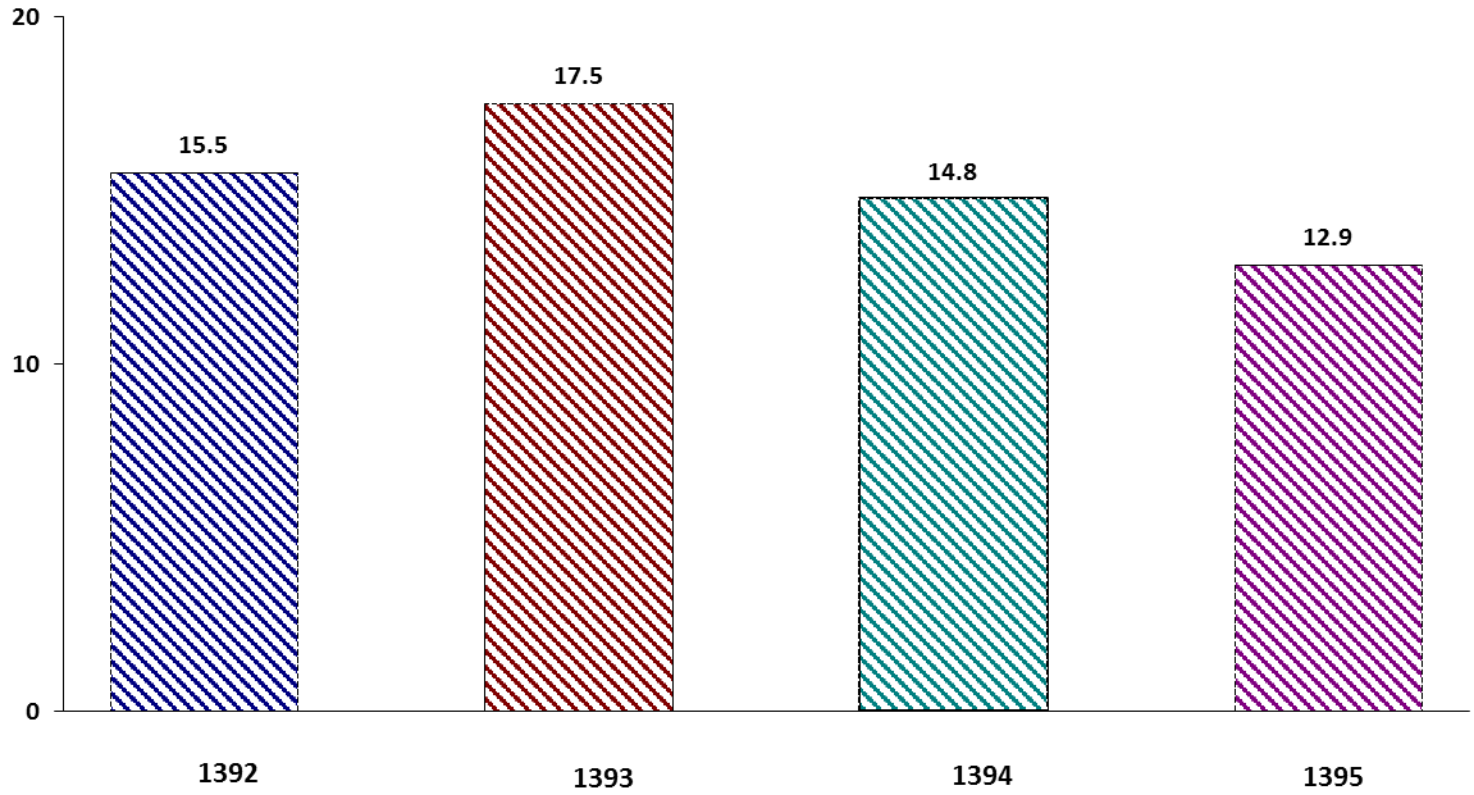


شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درکرمان(95-1392)

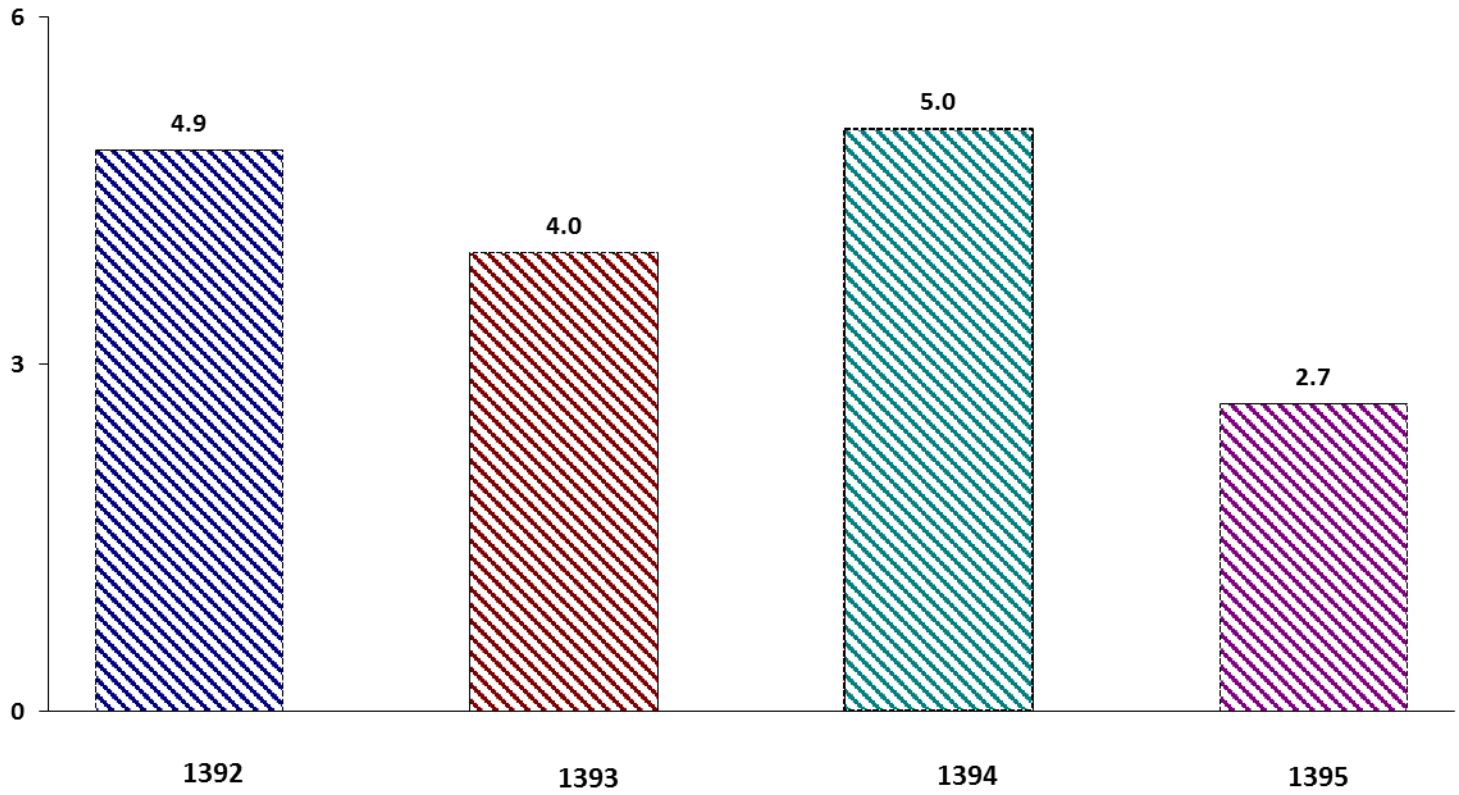


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درکرمان(95-1392)

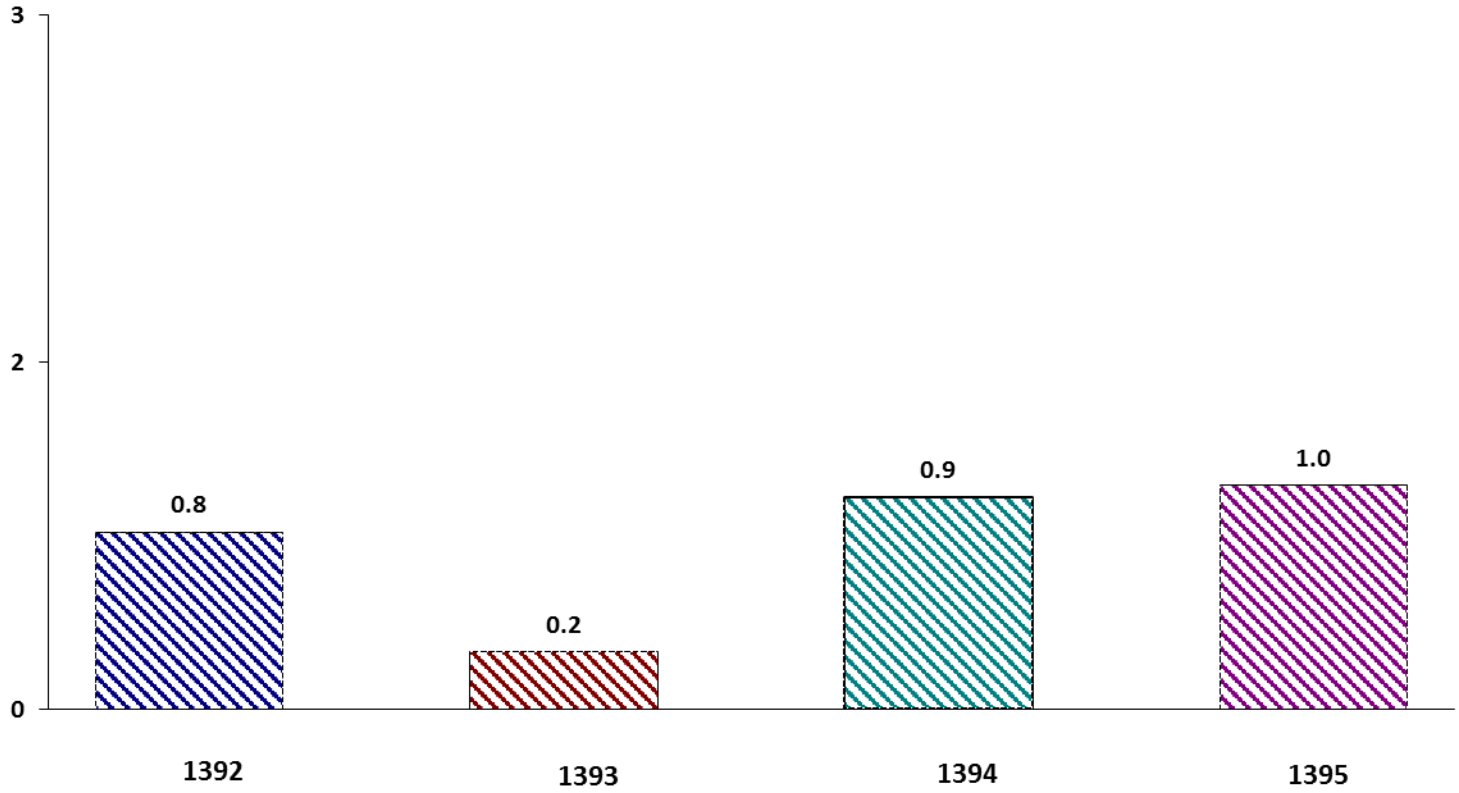
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درکرمان(95-1392)



شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درگلستان(95-1392)

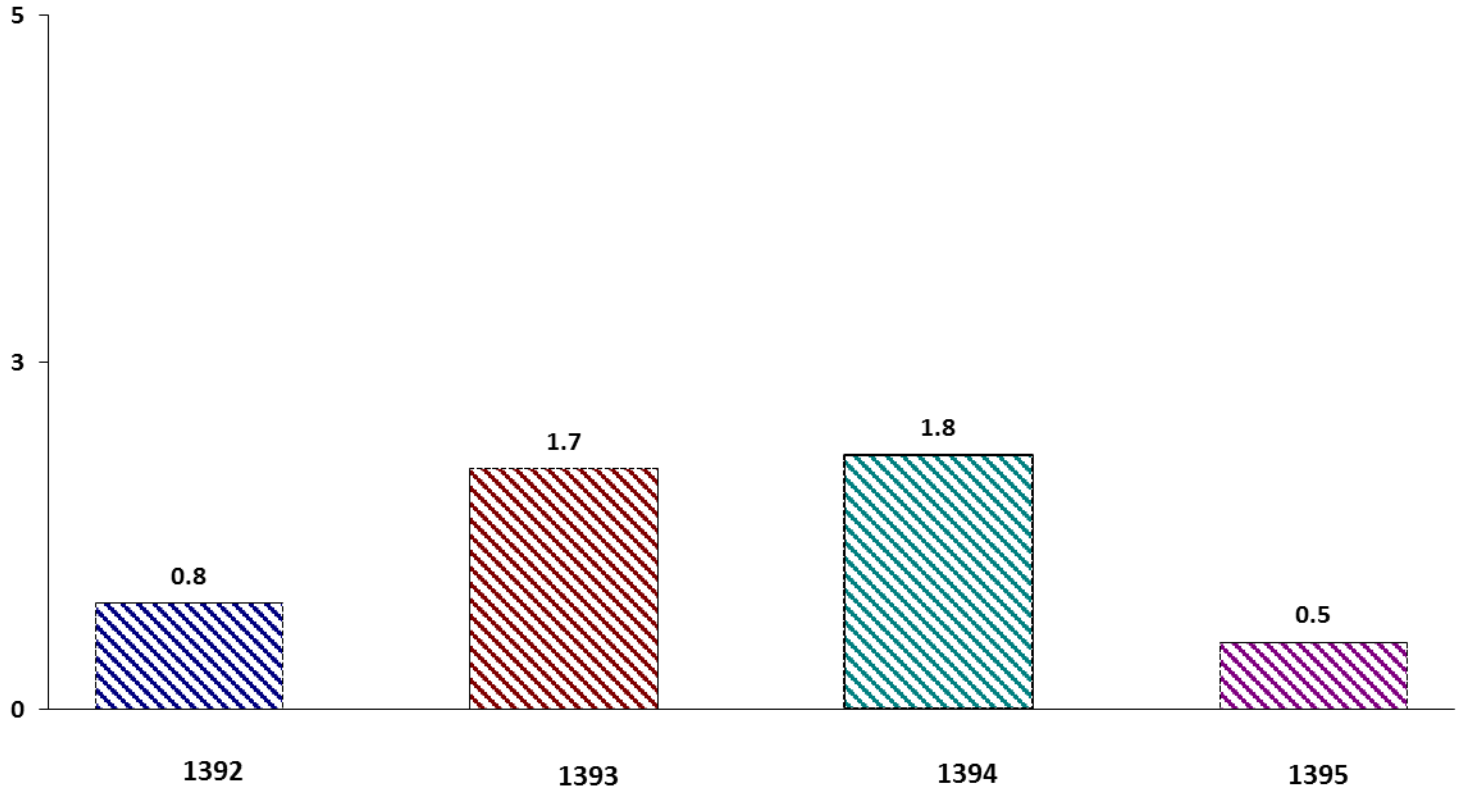


شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درگلستان(95-1392)

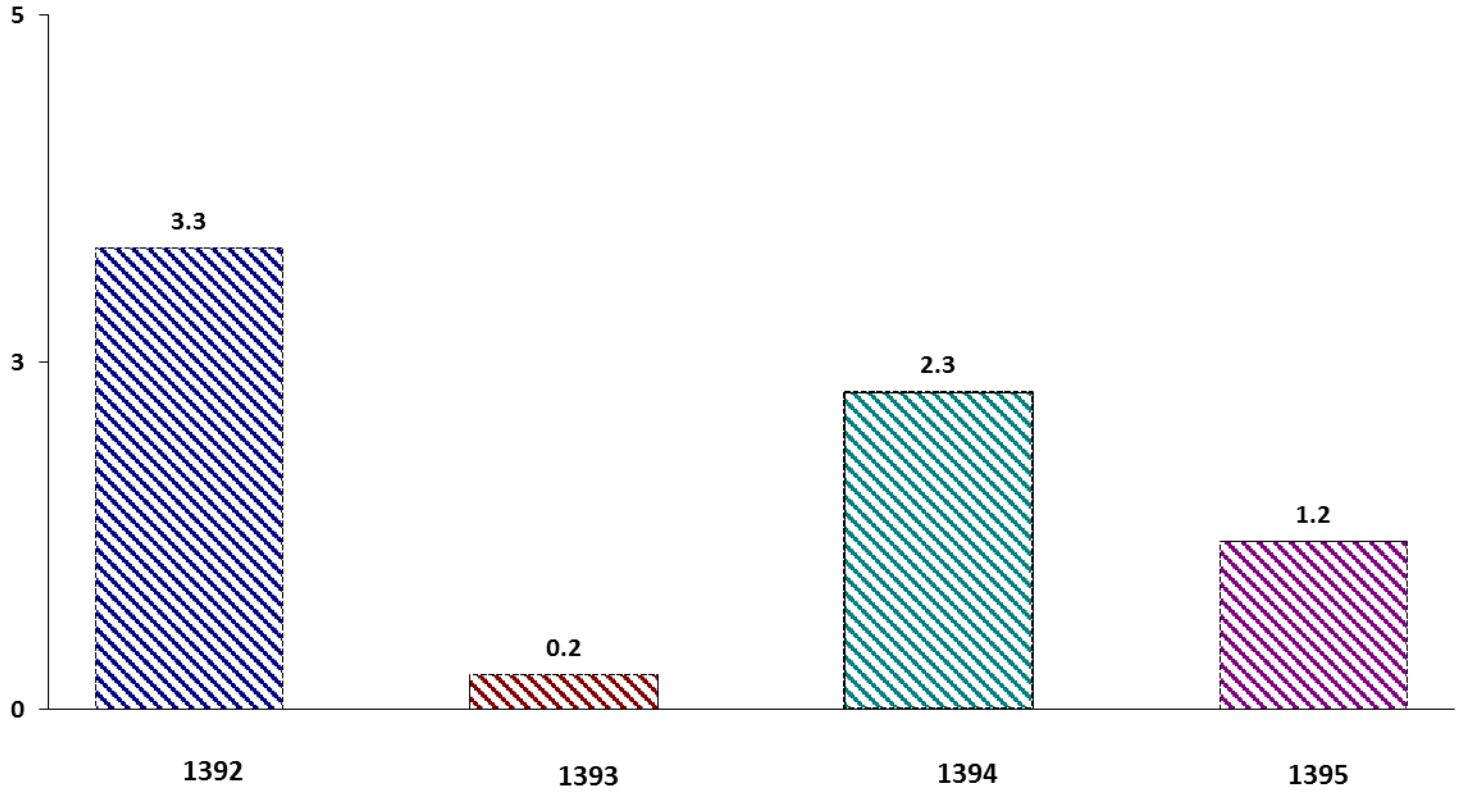


شیوع کلی ناهنجاری های مادرزادی عضلاني و اسكلتي(در هر ده هزار تولد) درگلستان(95-1392)

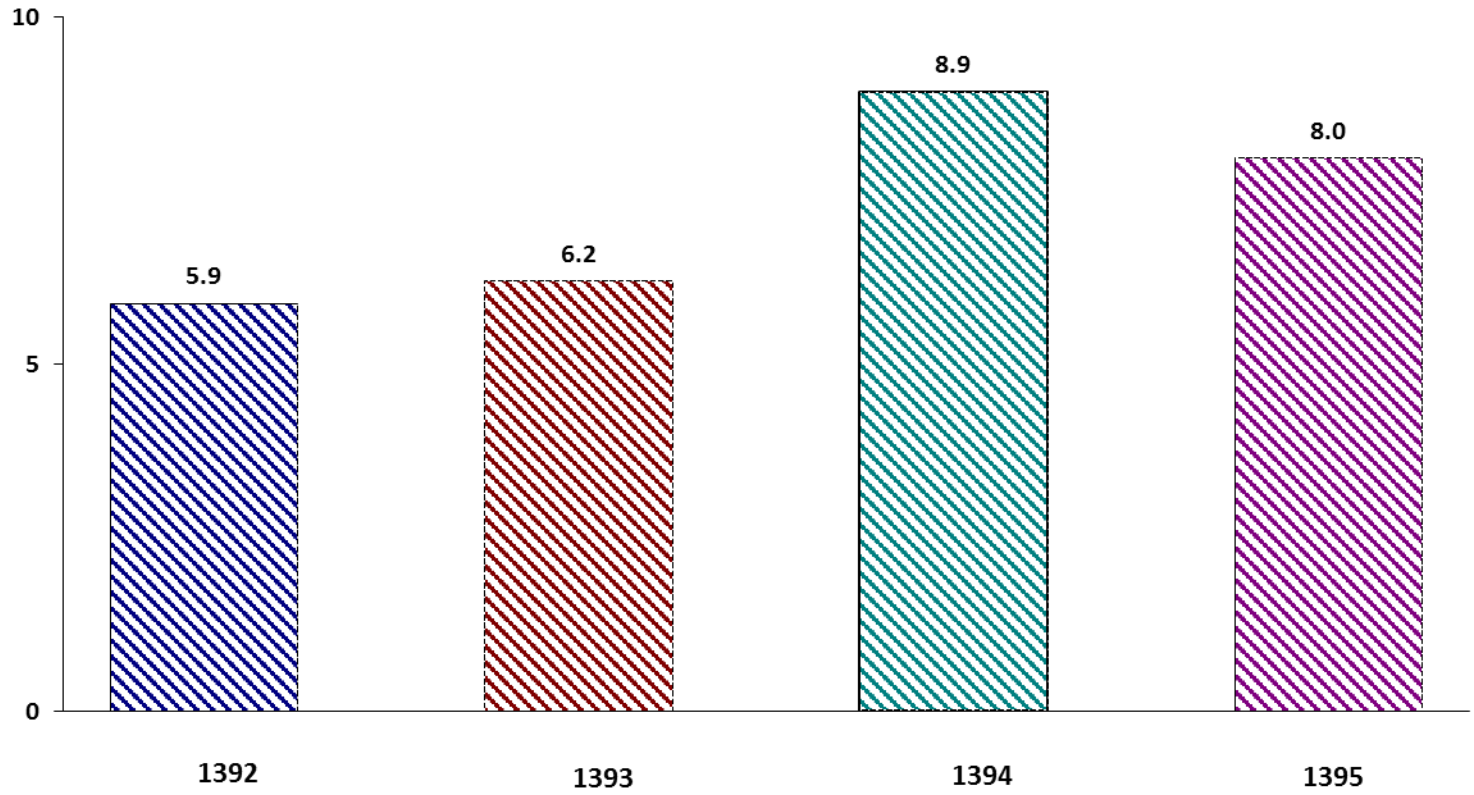
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درگلستان(95-1392)



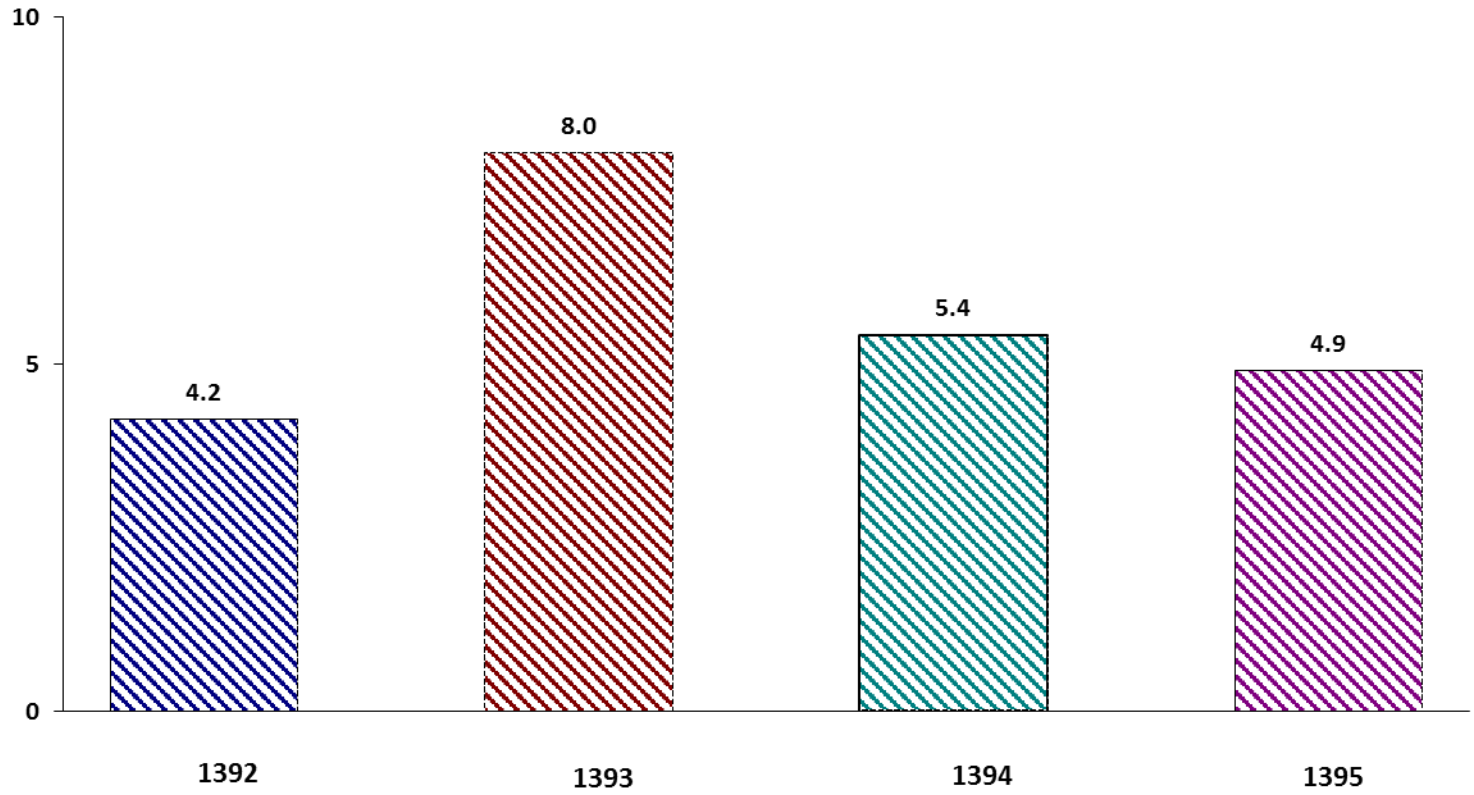
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درگلستان(95-1392)



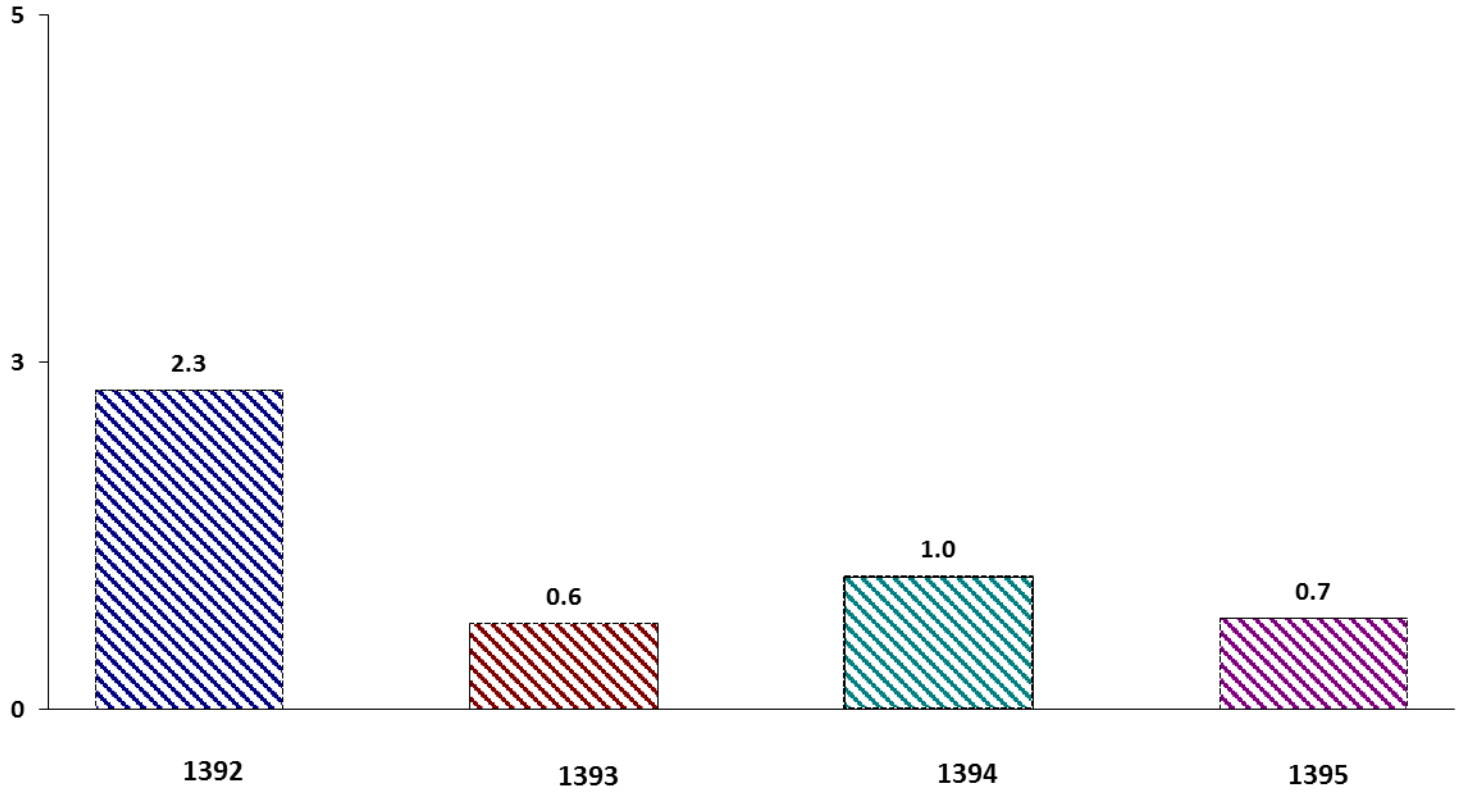
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درگلستان(95-1392)



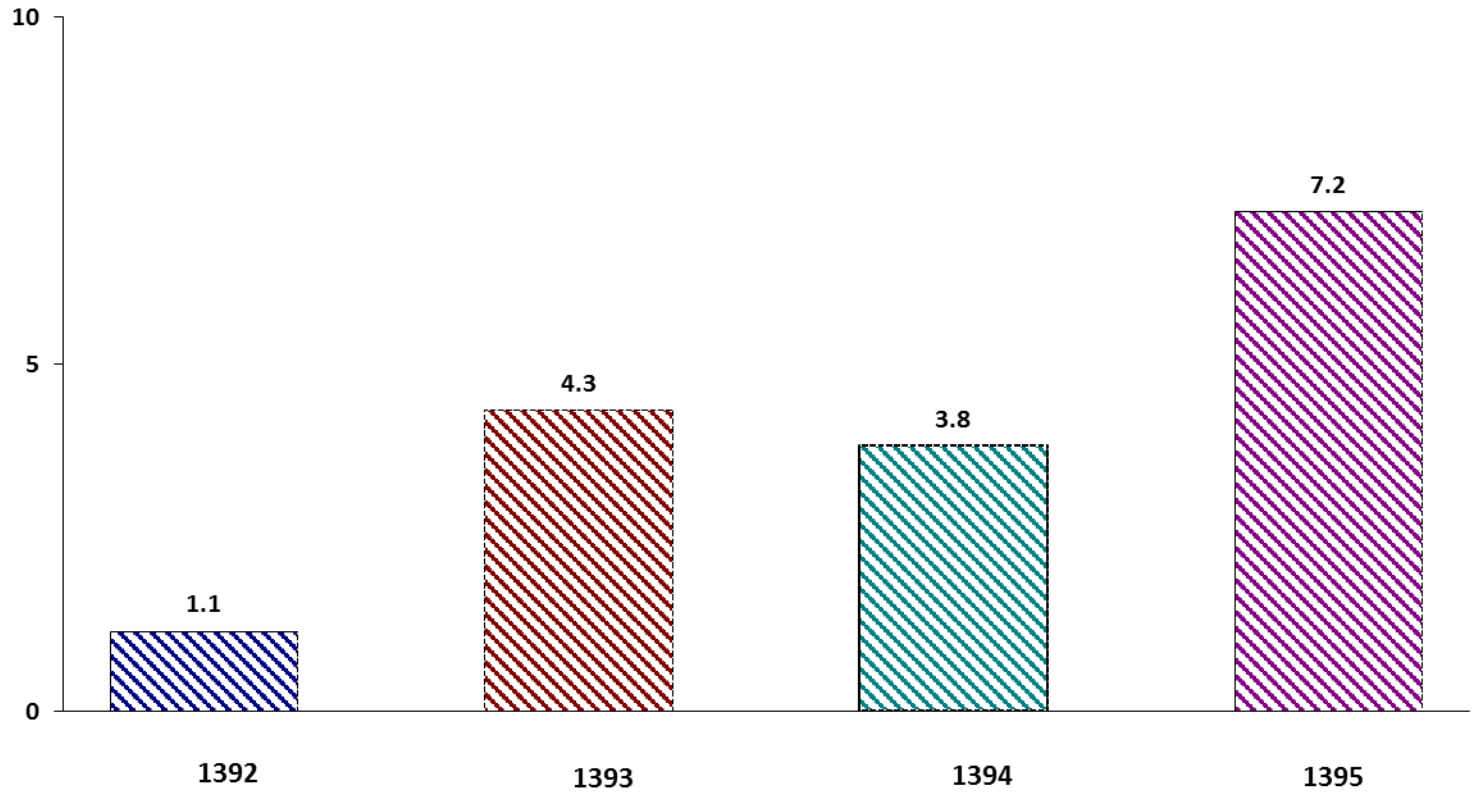
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درگیلان(95-1392)



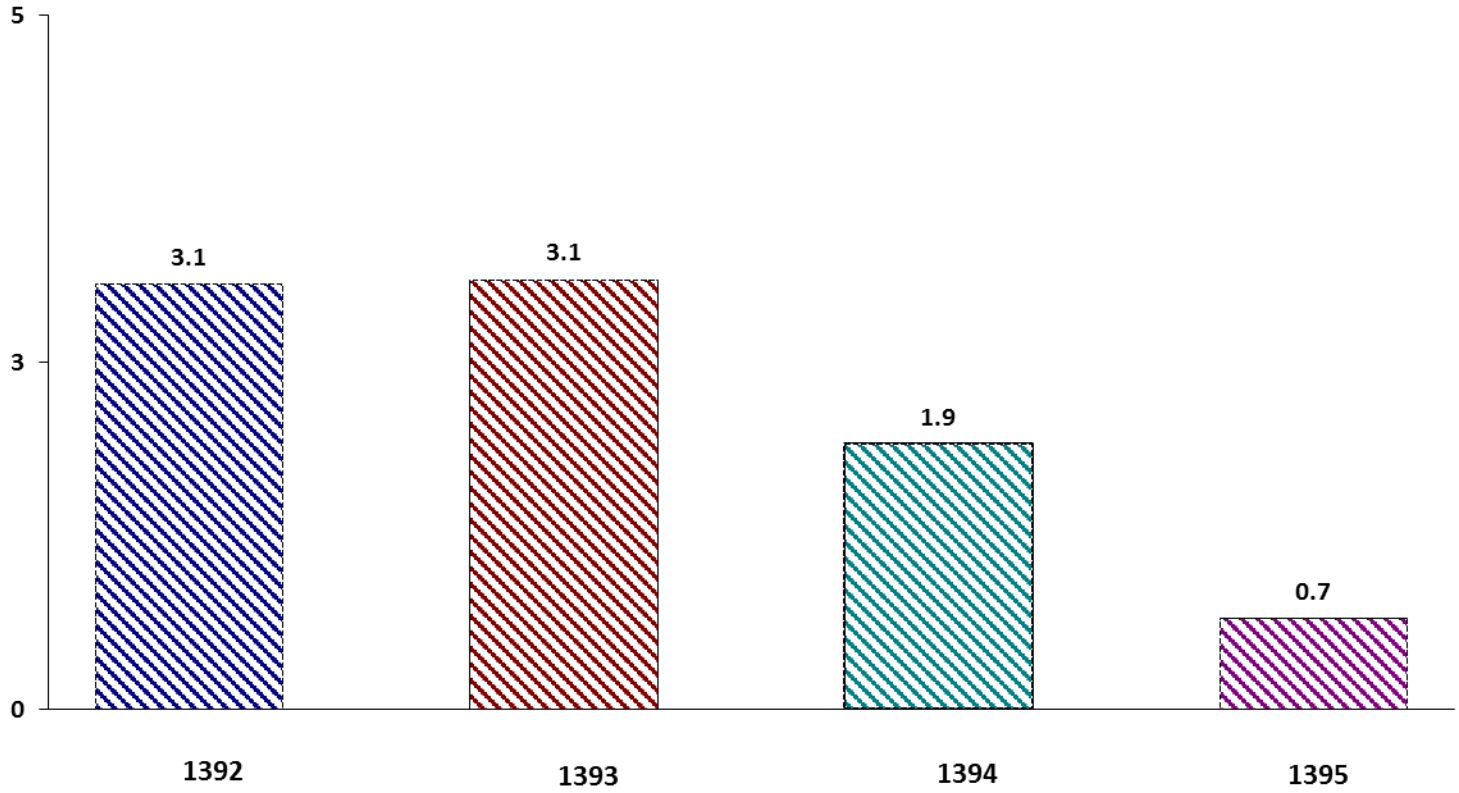
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درگیلان(95-1392)



شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درگیلان(95-1392)

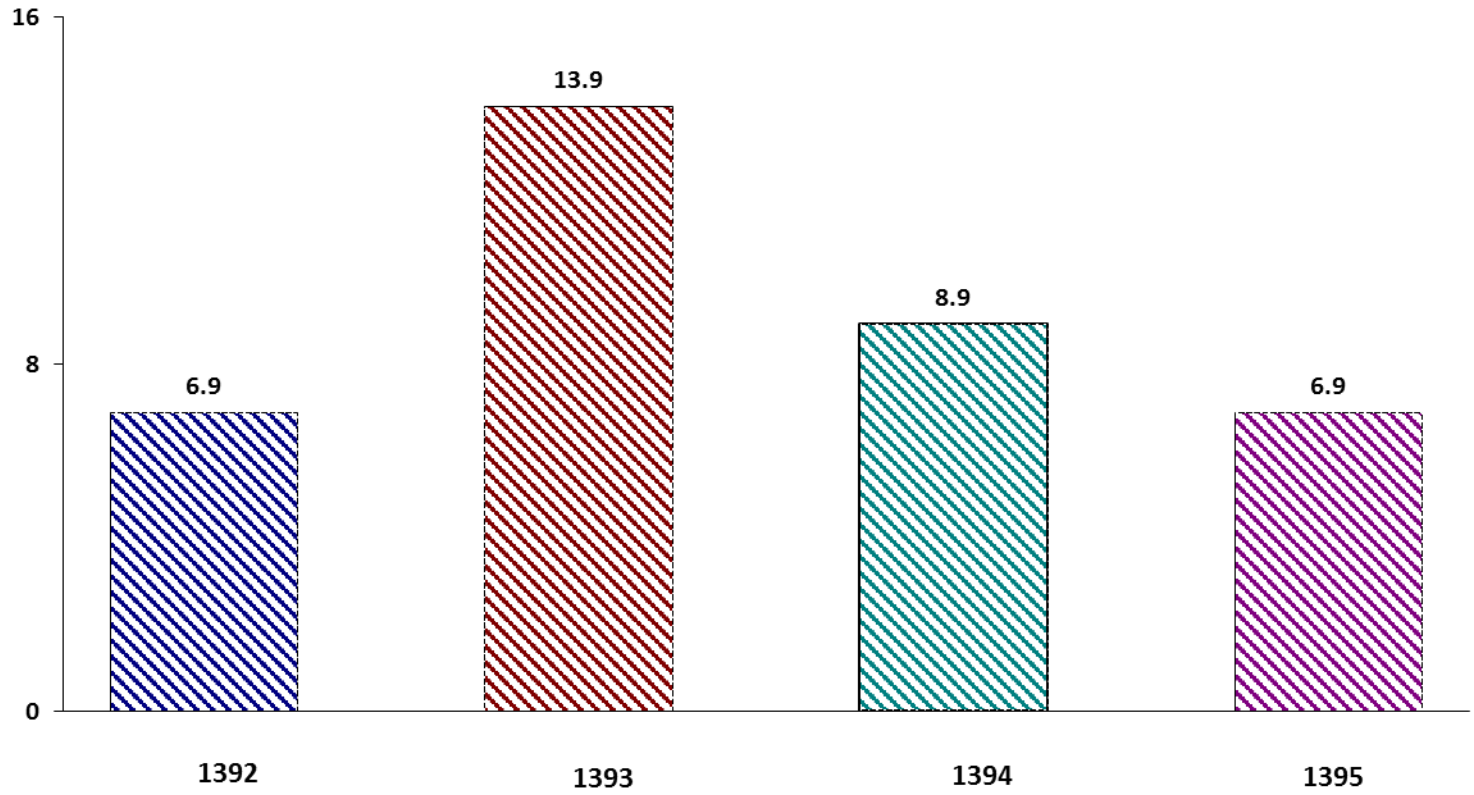


شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درگیلان(95-1392)

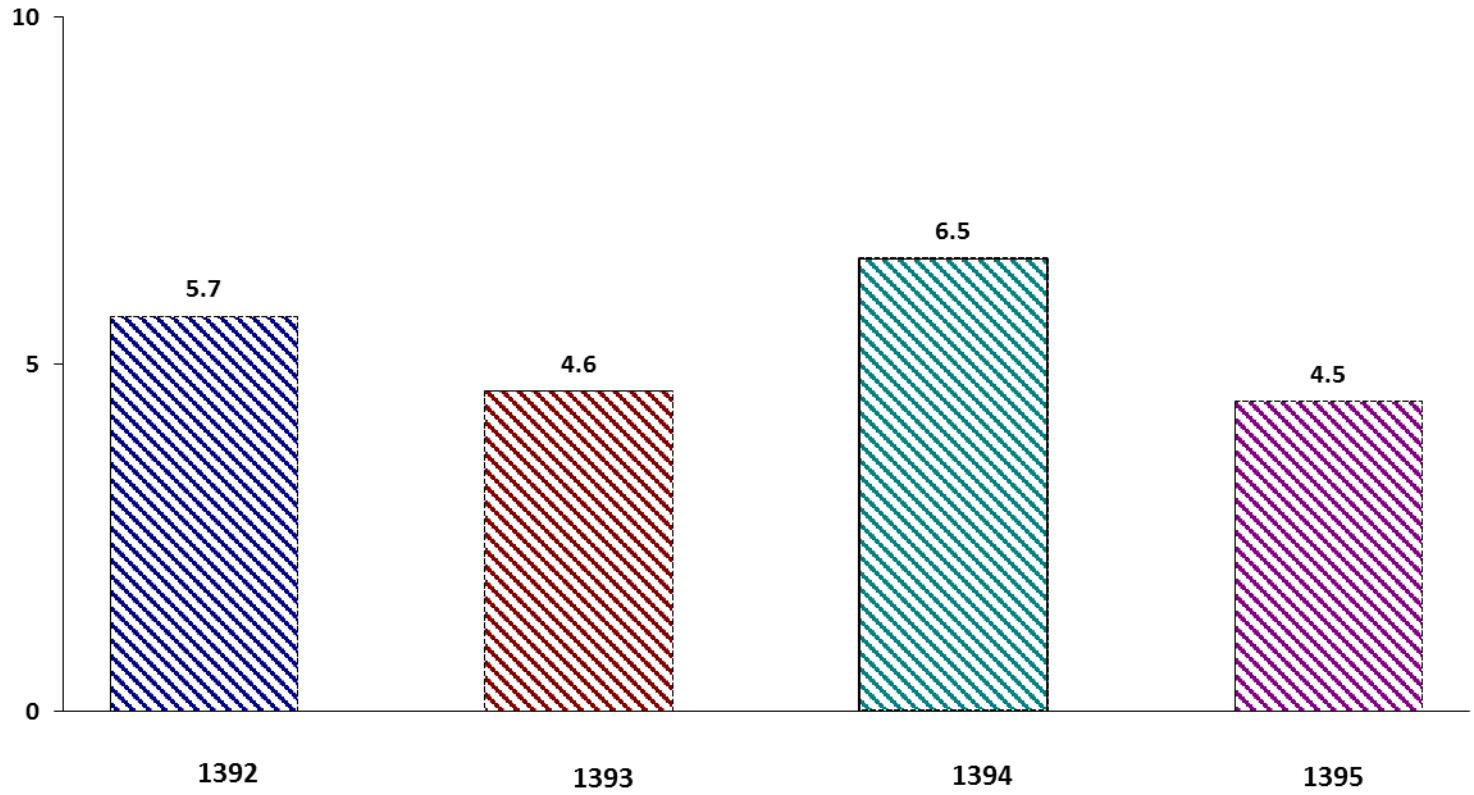


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درگیلان(95-1392)

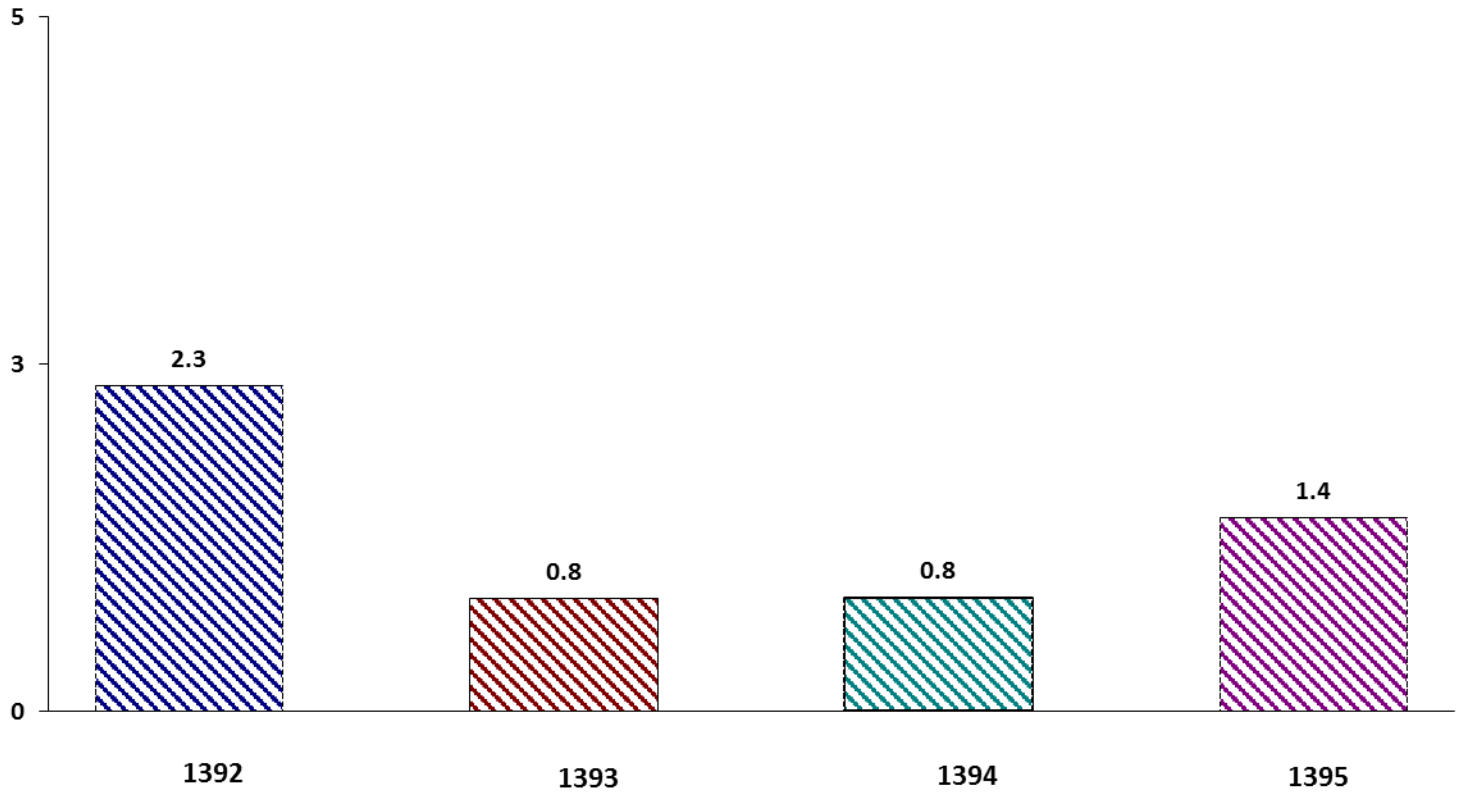
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درگیلان(95-1392)



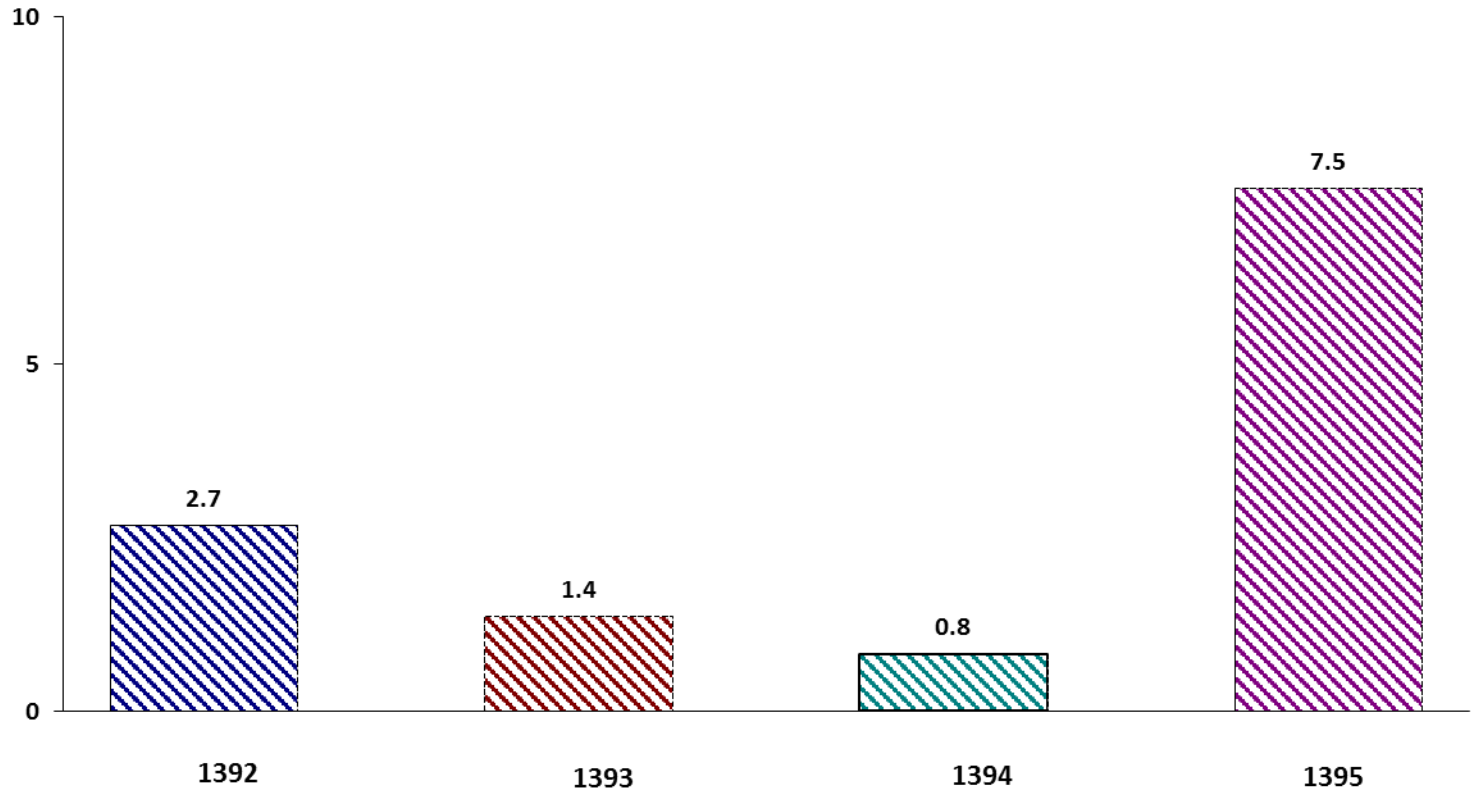
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درلرستان(95-1392)



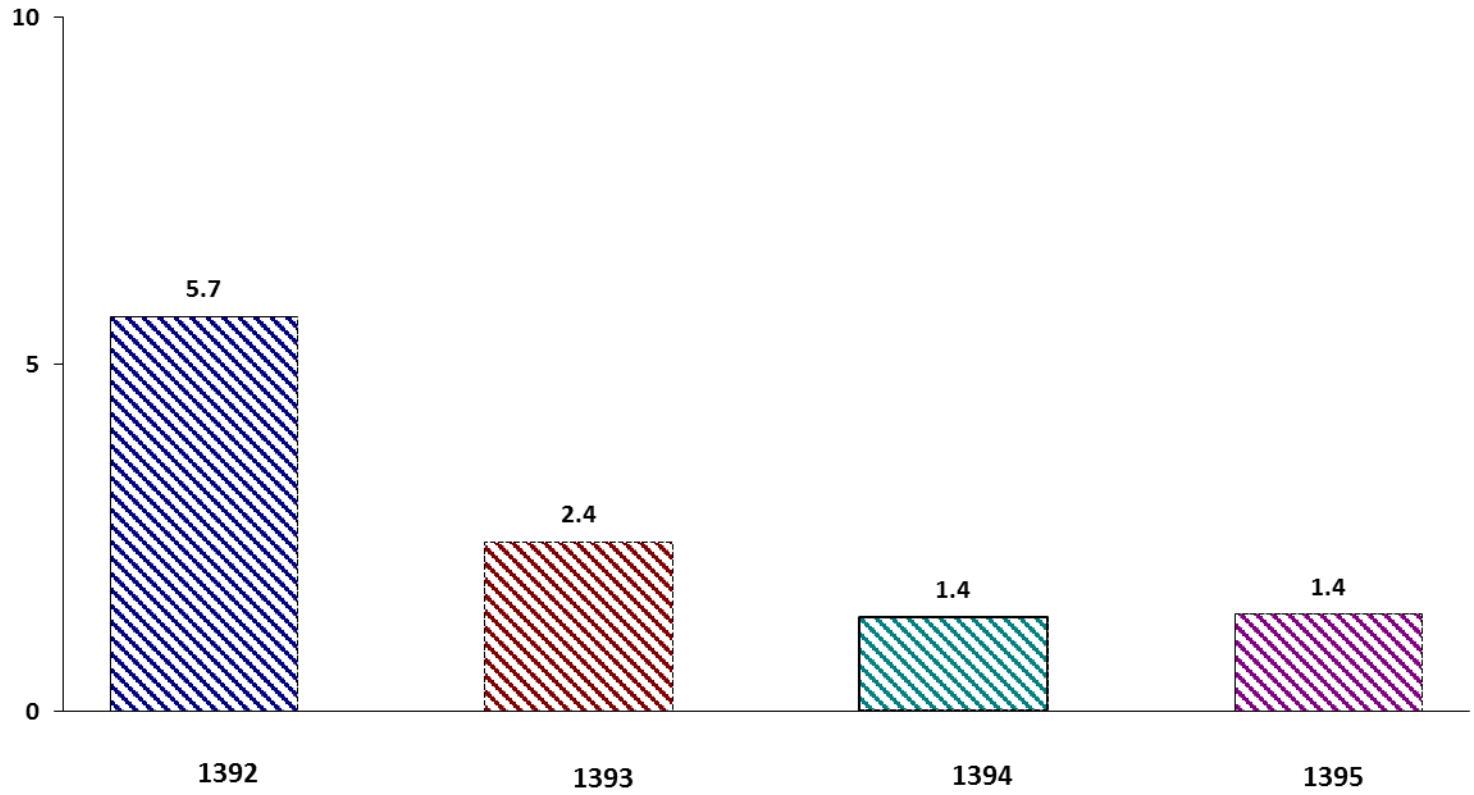
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درلرستان(95-1392)



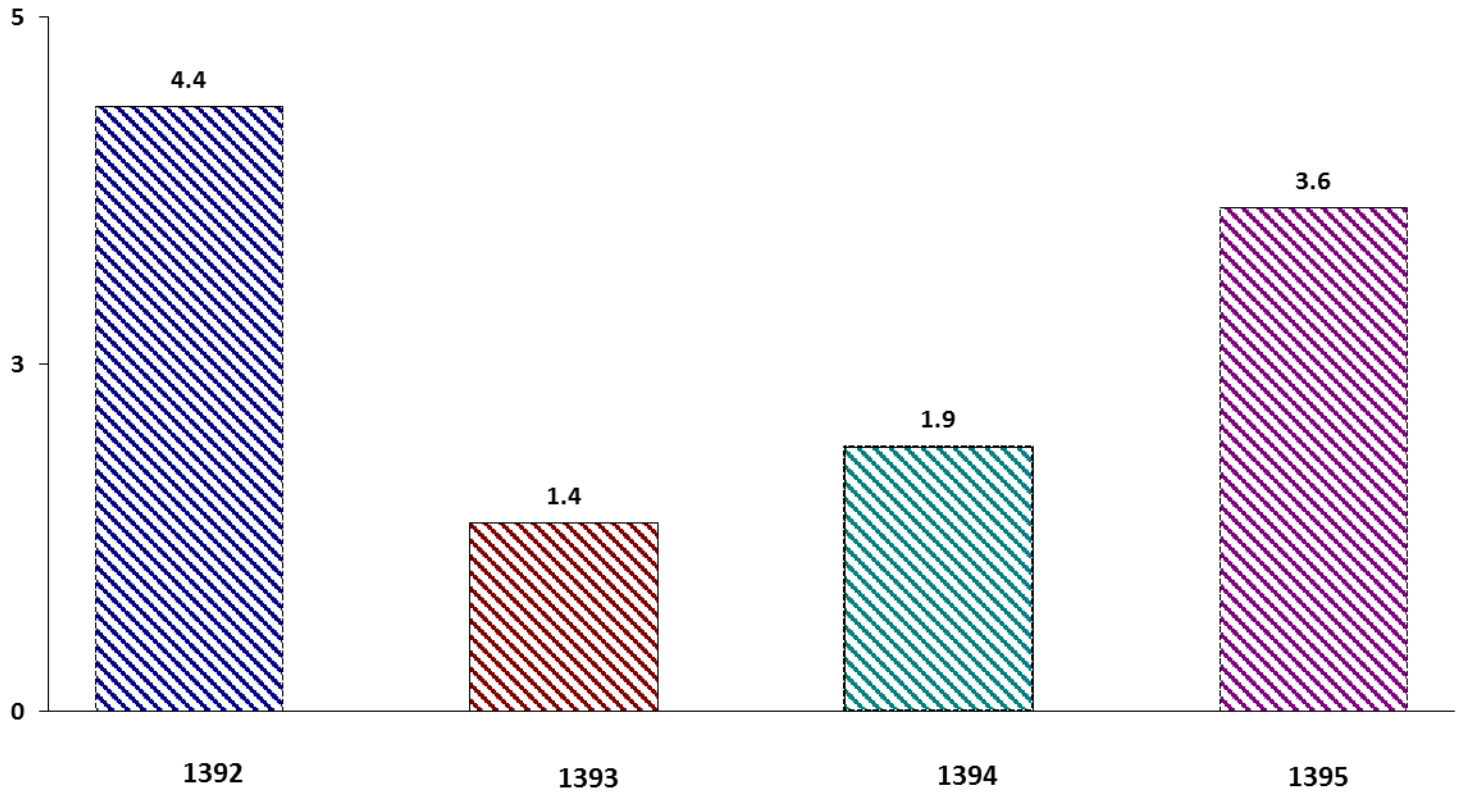
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درلرستان(95-1392)



شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درلرستان(95-1392)

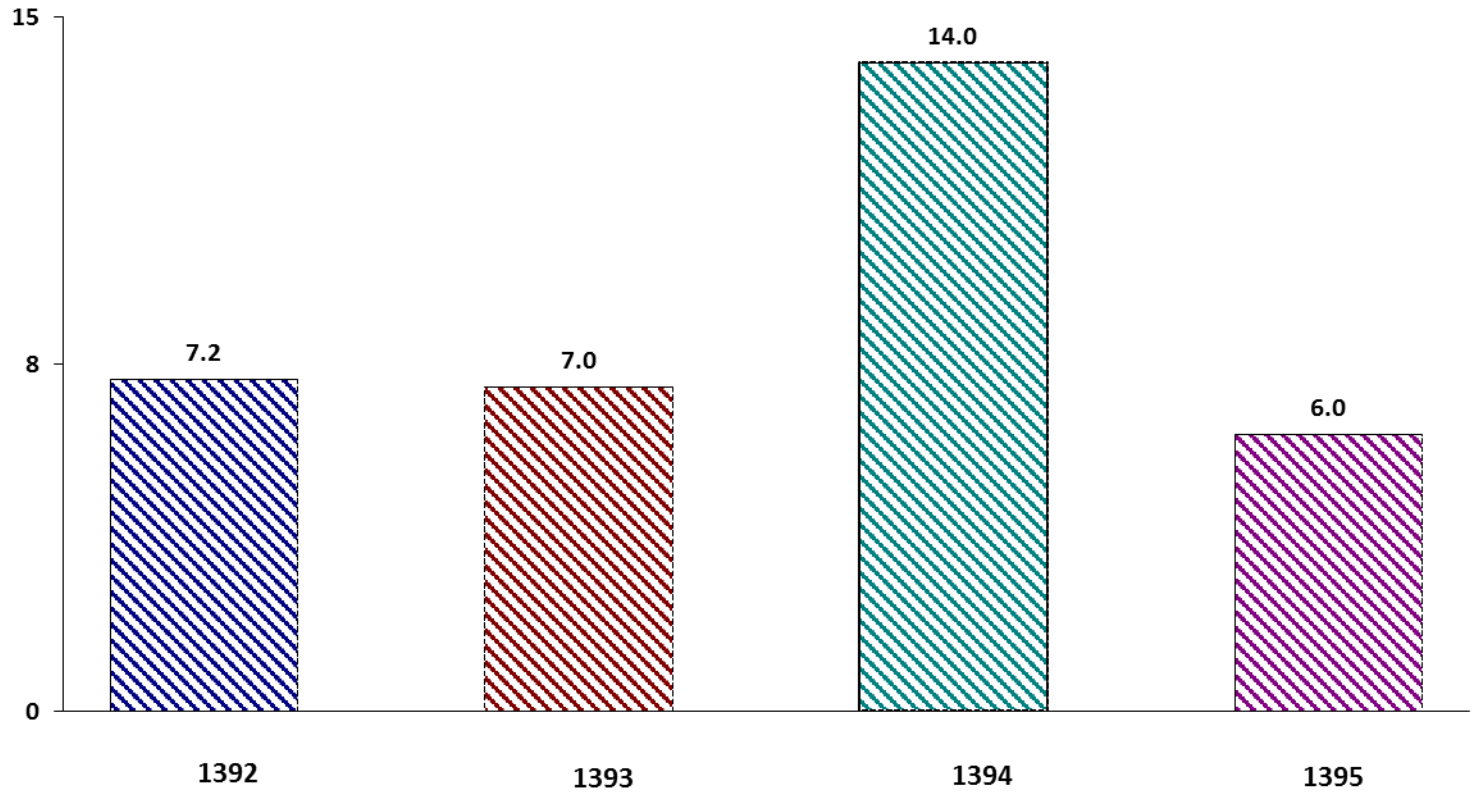


شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درلرستان(95-1392)

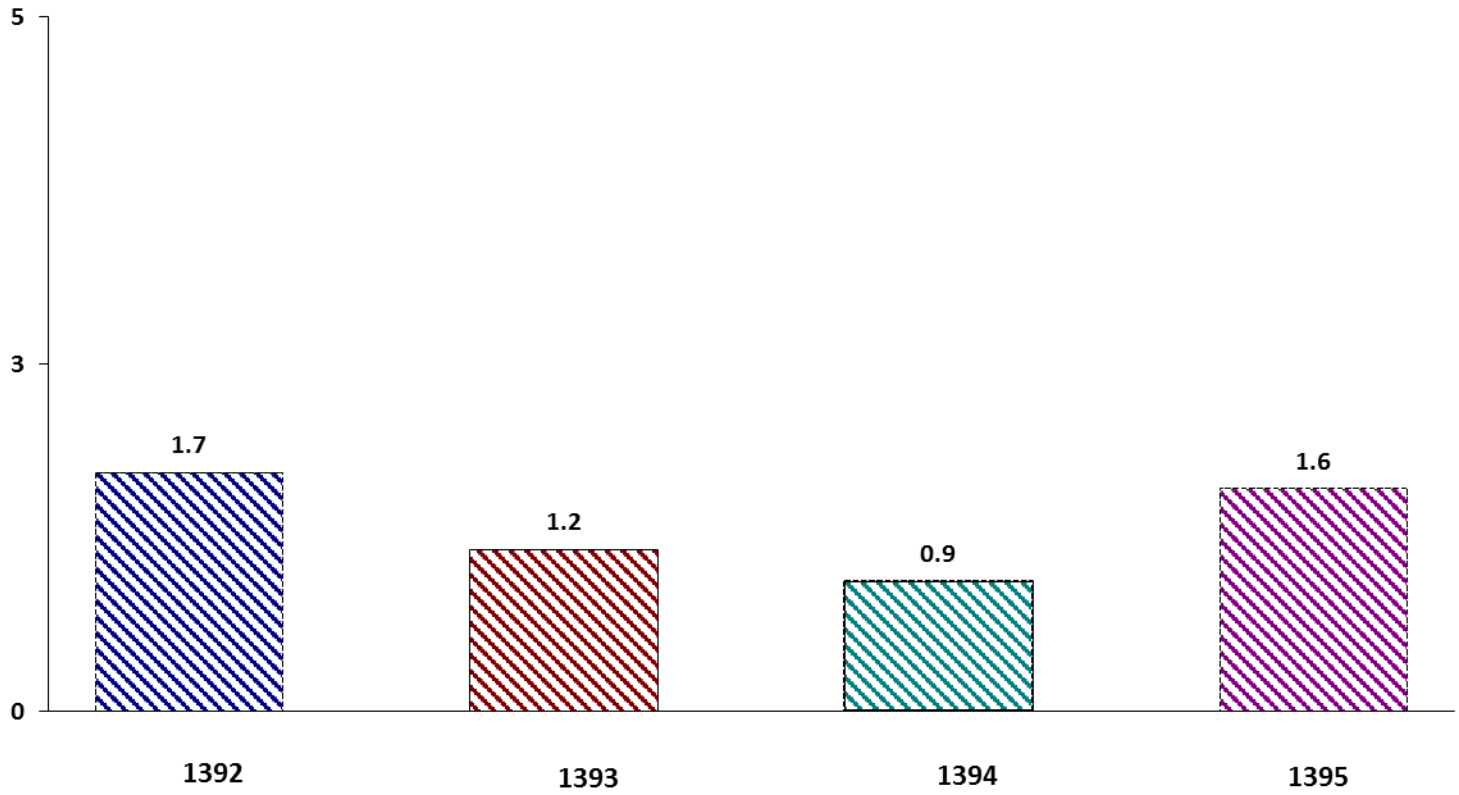


شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درلرستان(95-1392)

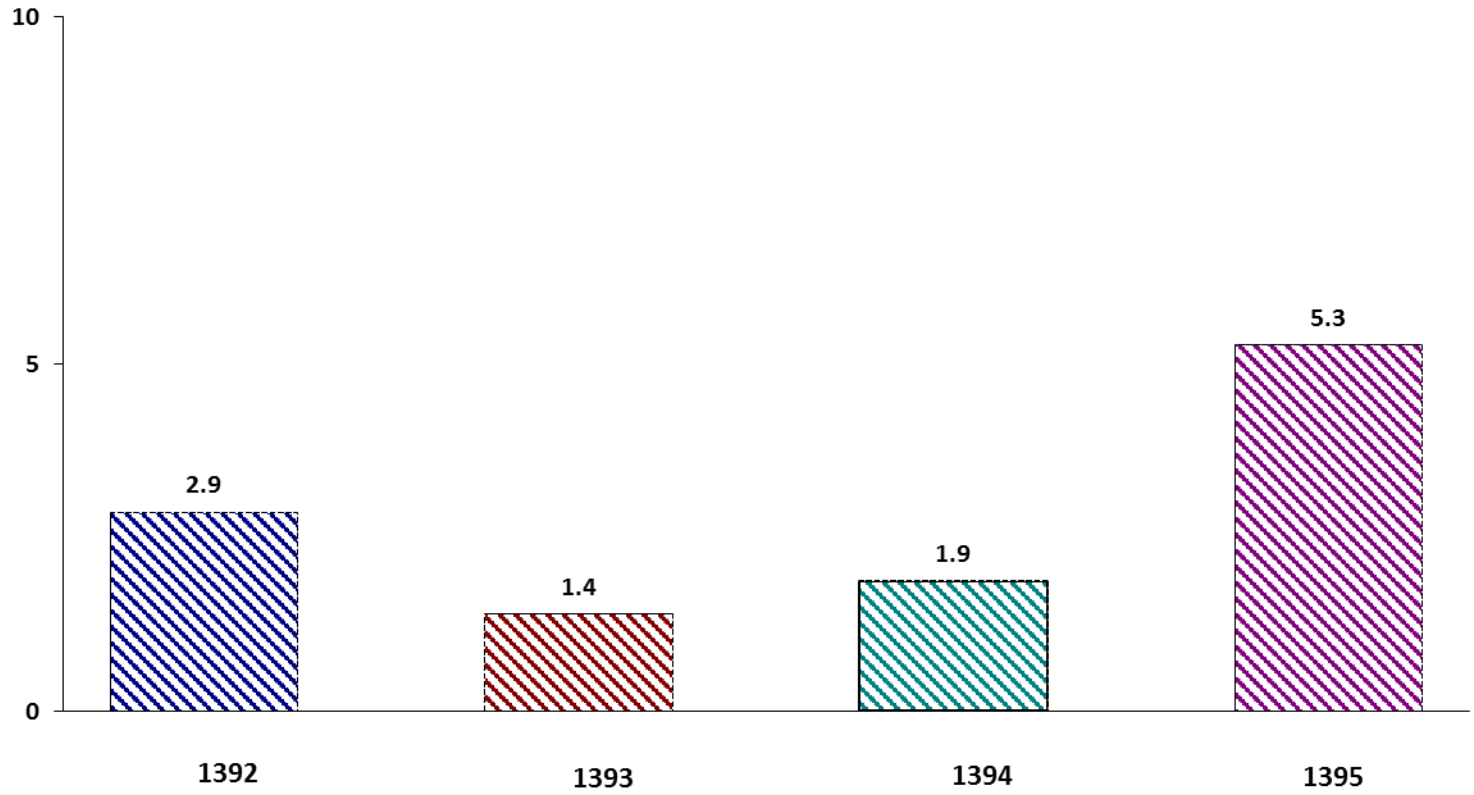
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درمازندران(95-1392)



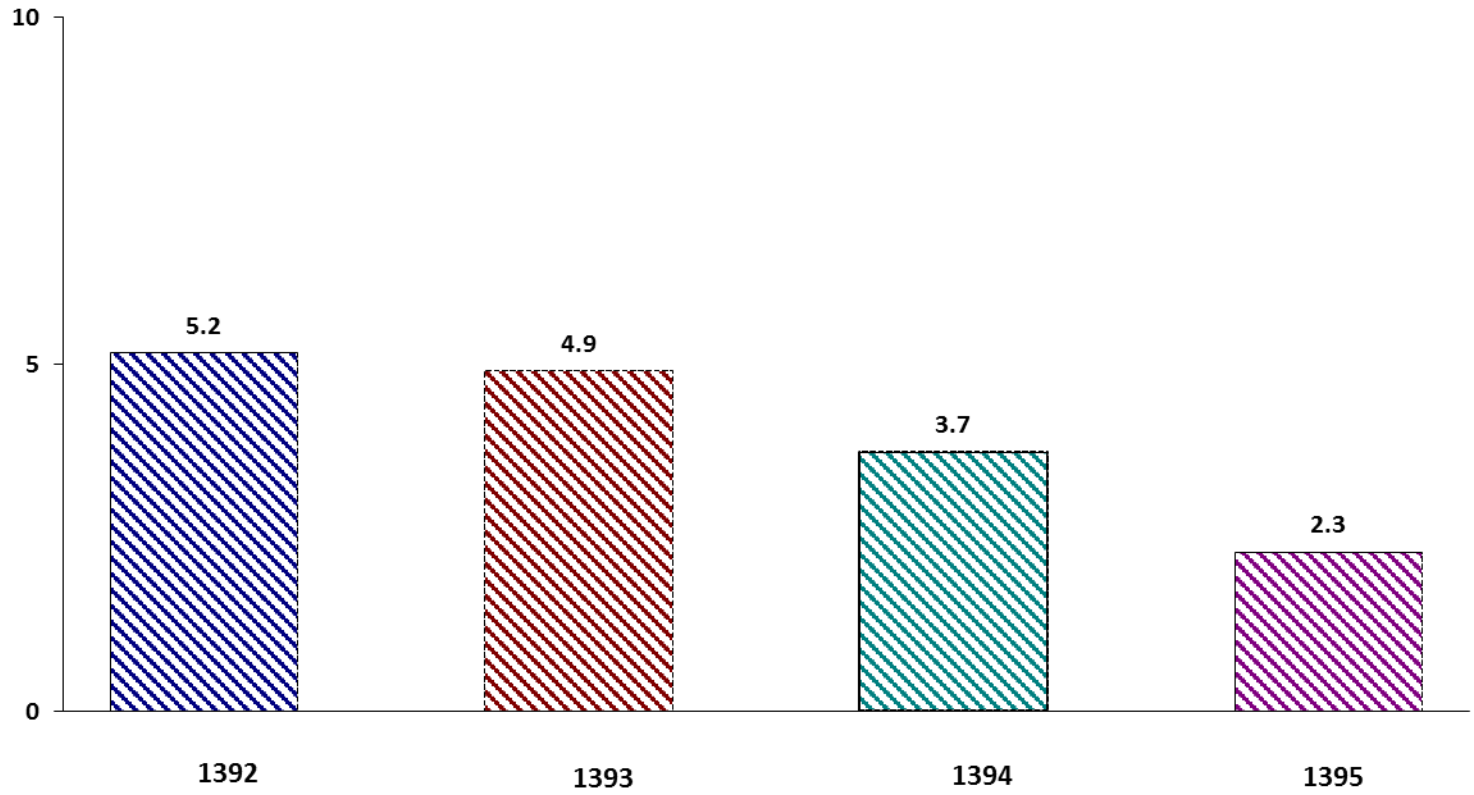
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درمازندران(95-1392)



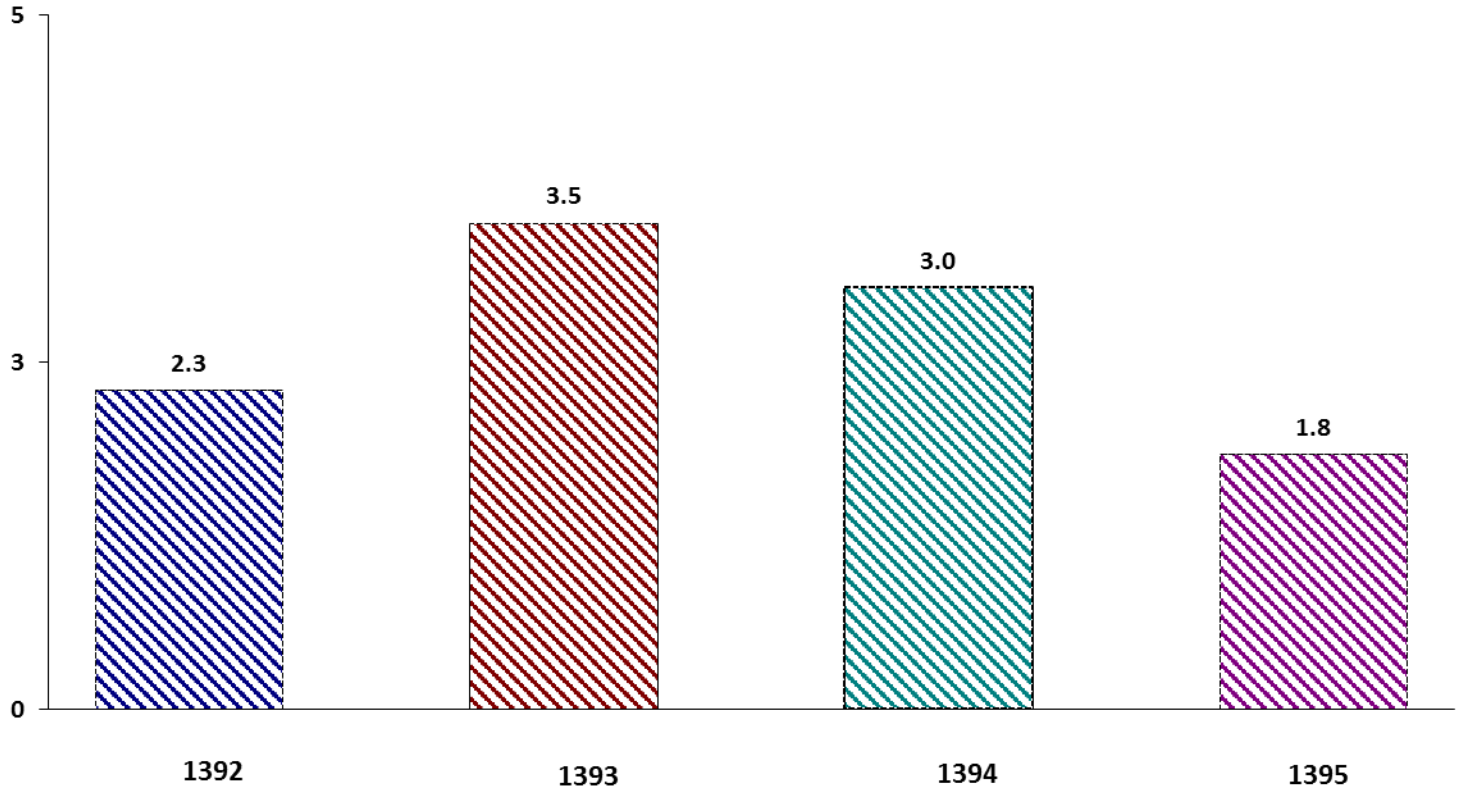
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درمازندران(95-1392)



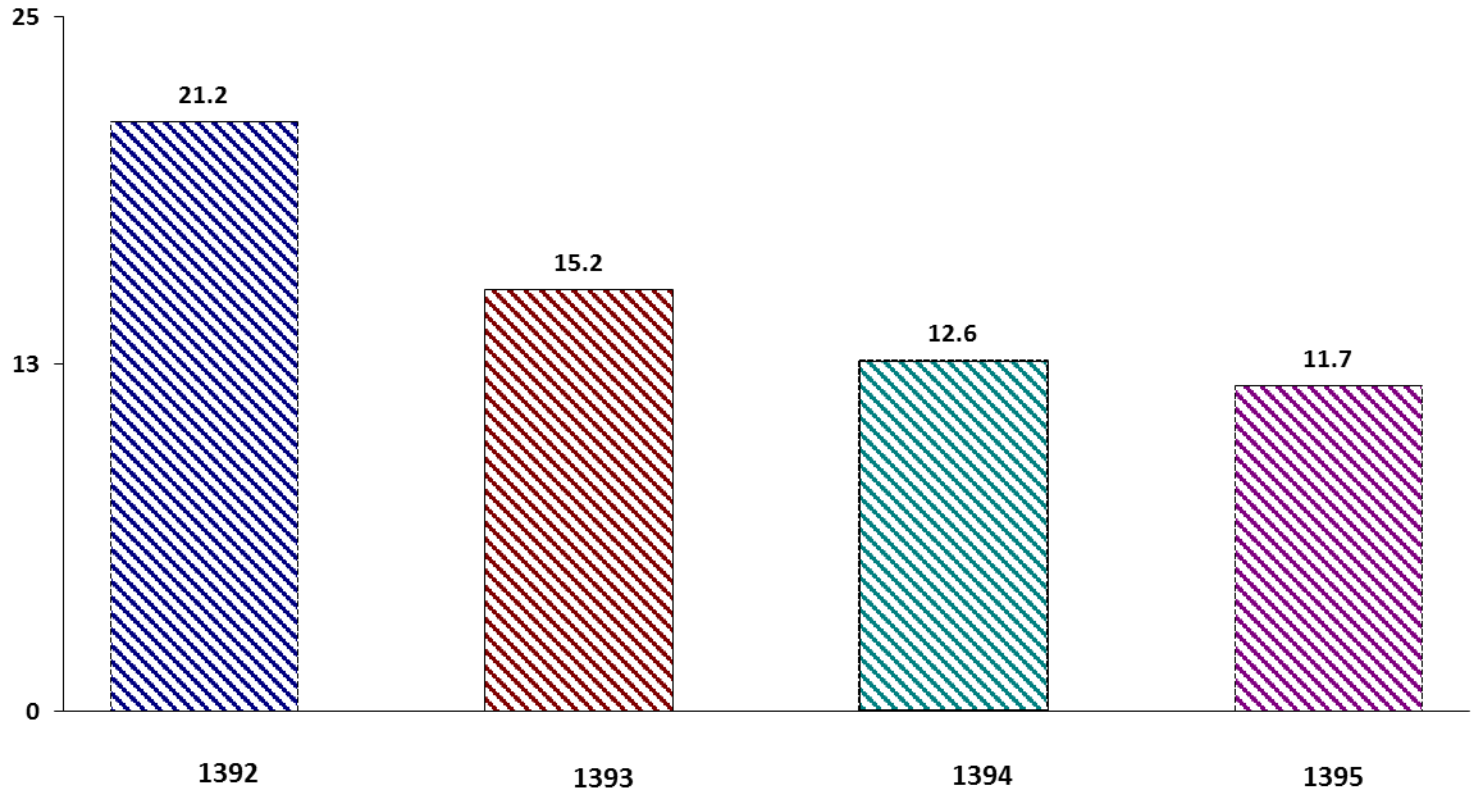
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درمازندران(95-1392)



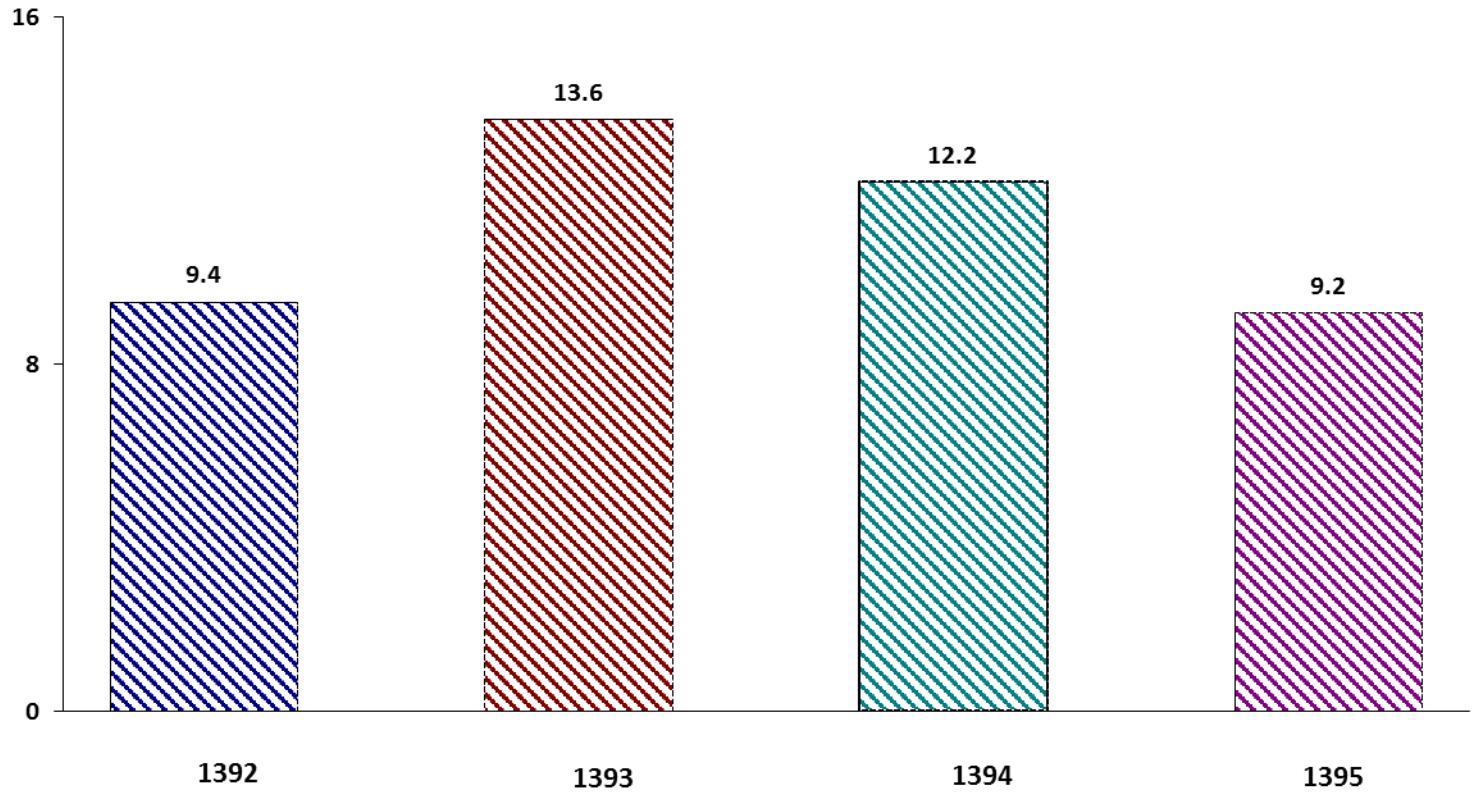
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درمازندران(95-1392)



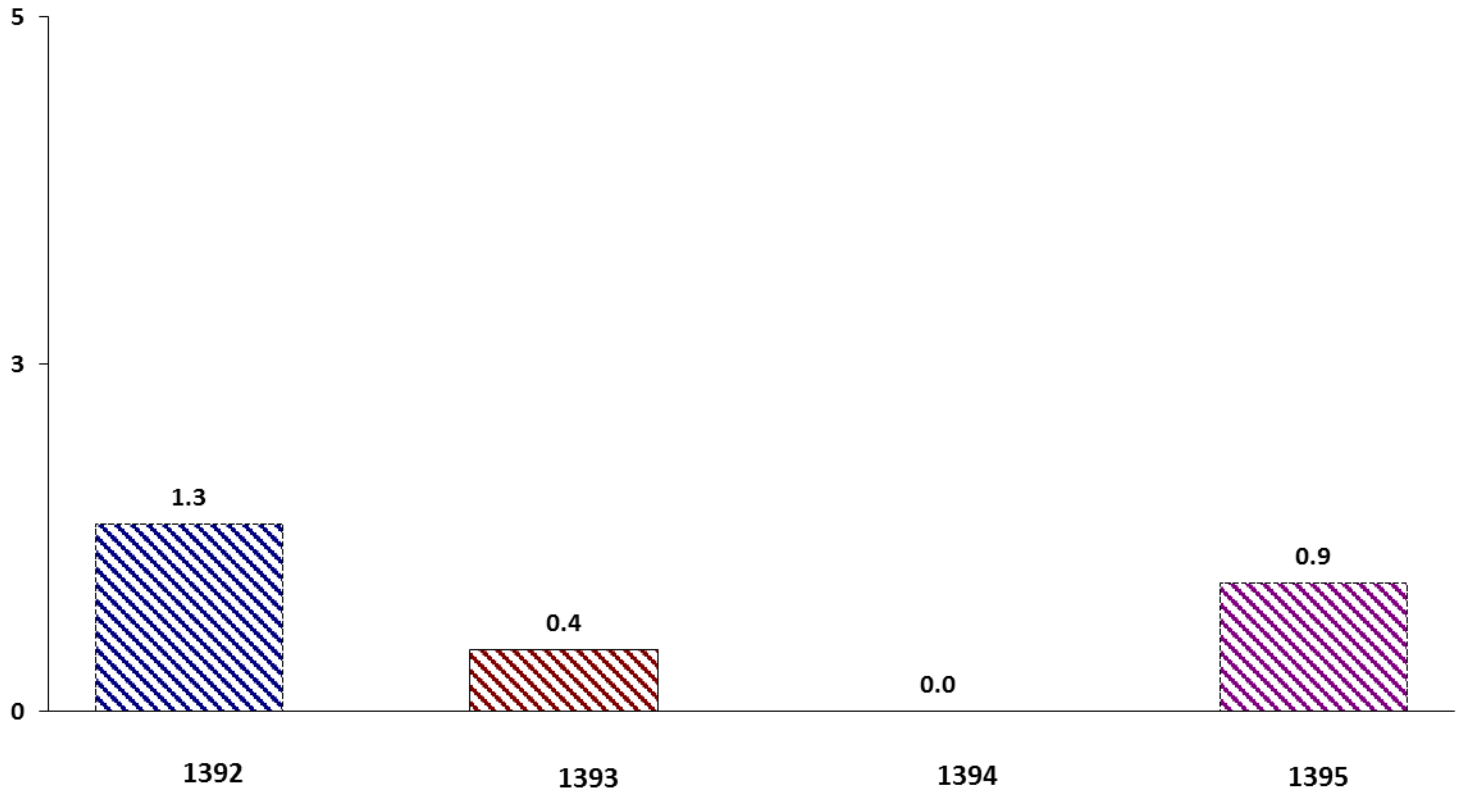
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درمازندران(95-1392)



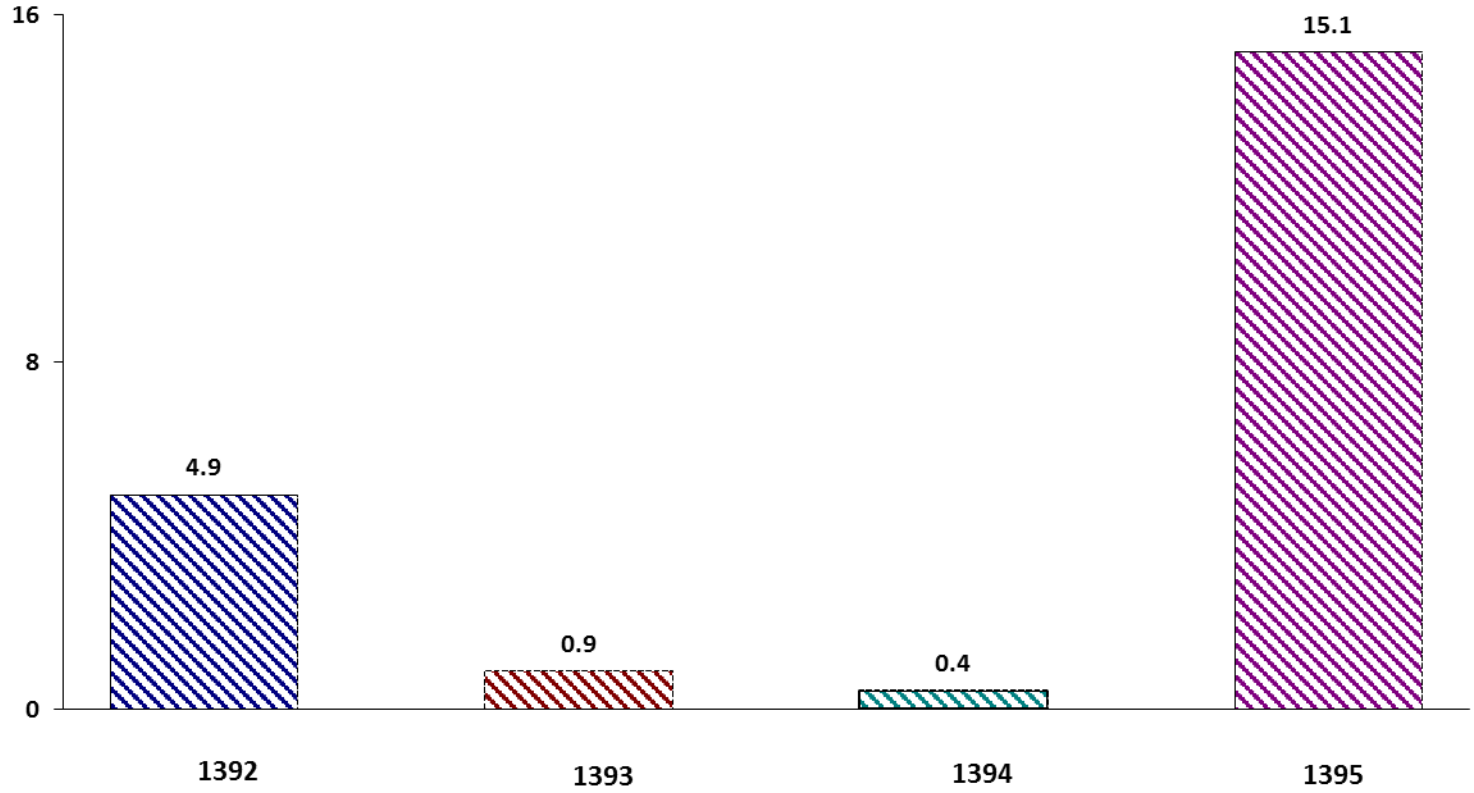
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درمرکزي(95-1392)



شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درمرکزي(95-1392)

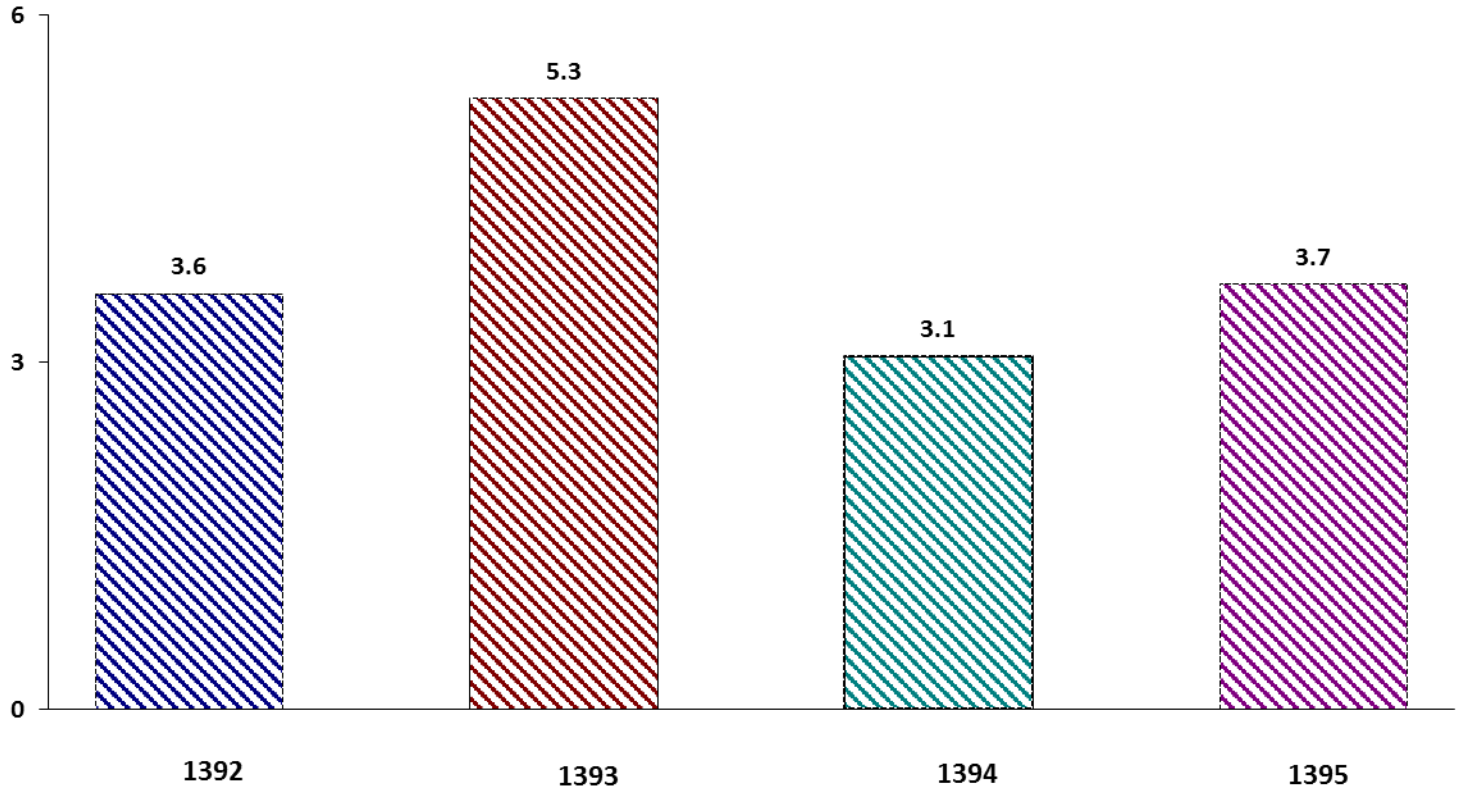


شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درمرکزي(95-1392)

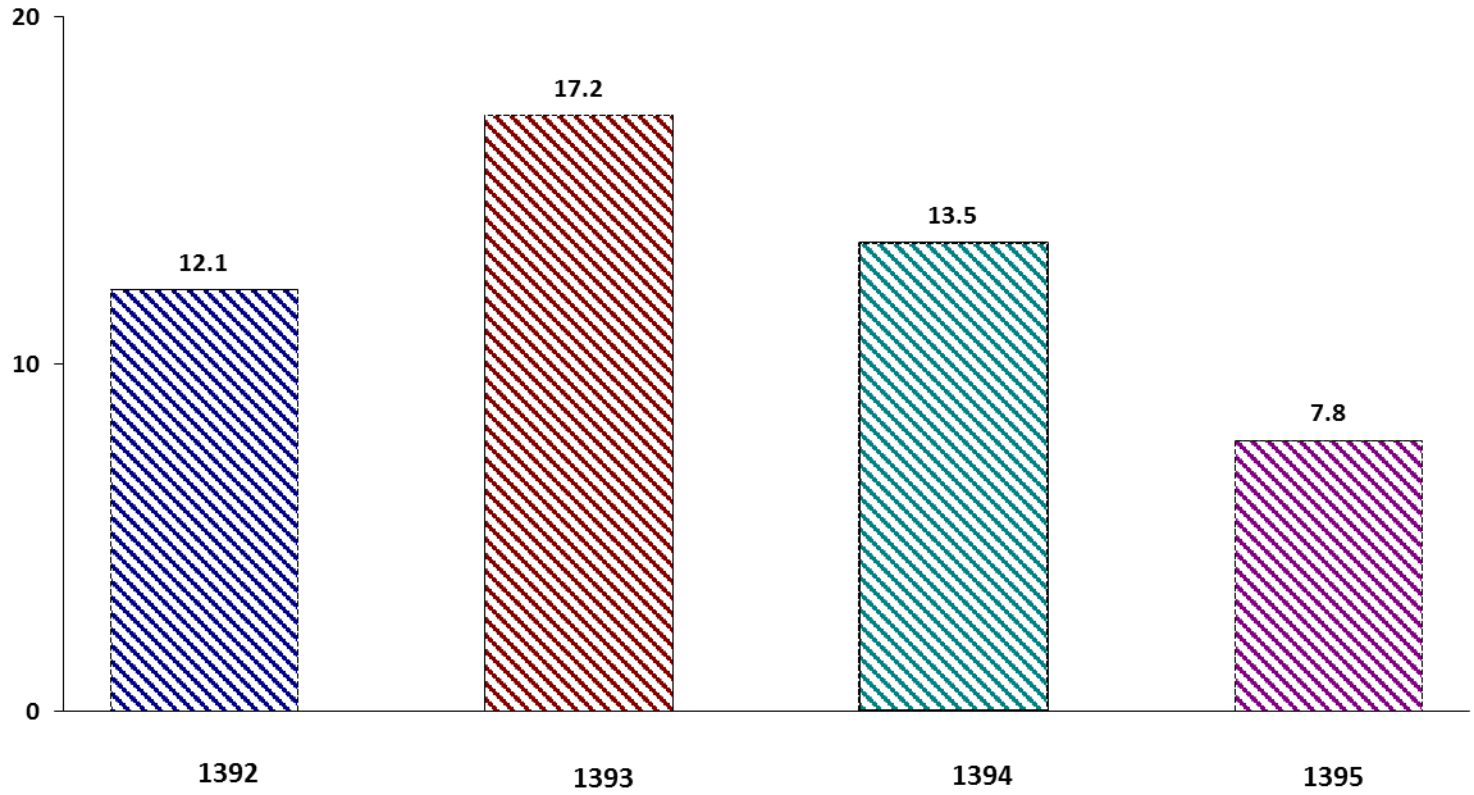


شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درمرکزي(95-1392)

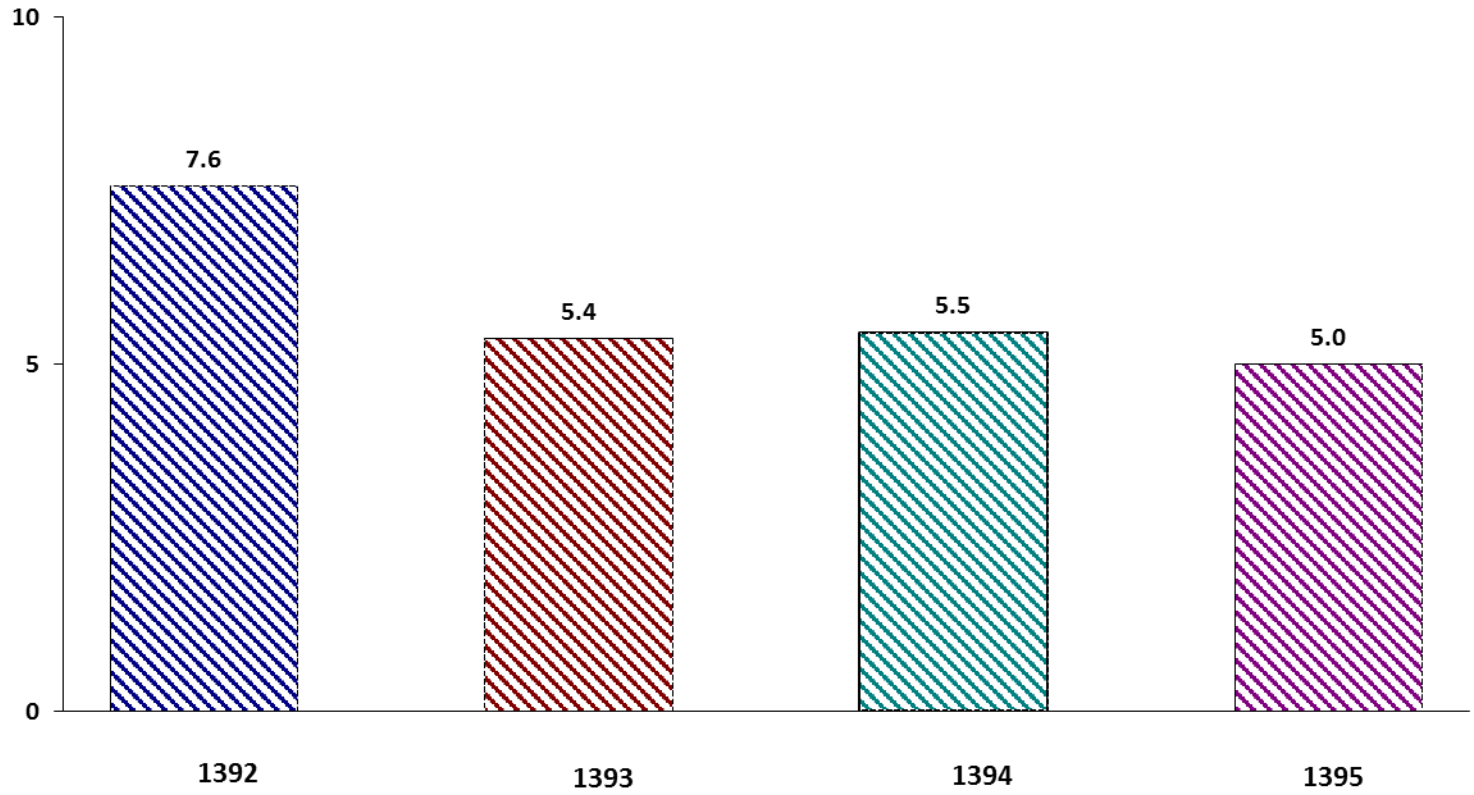
شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درمرکزي(95-1392)



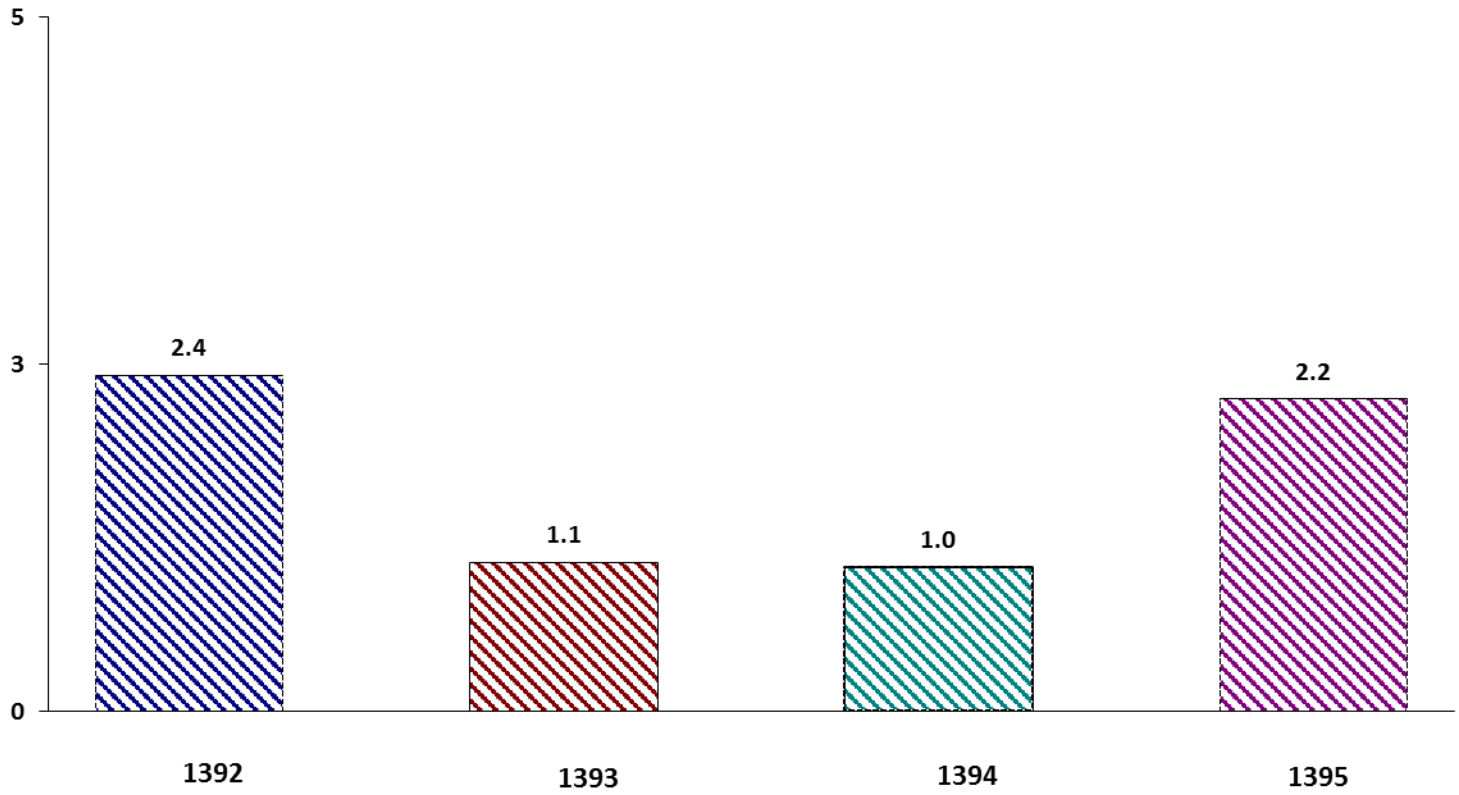
شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درمرکزي(95-1392)



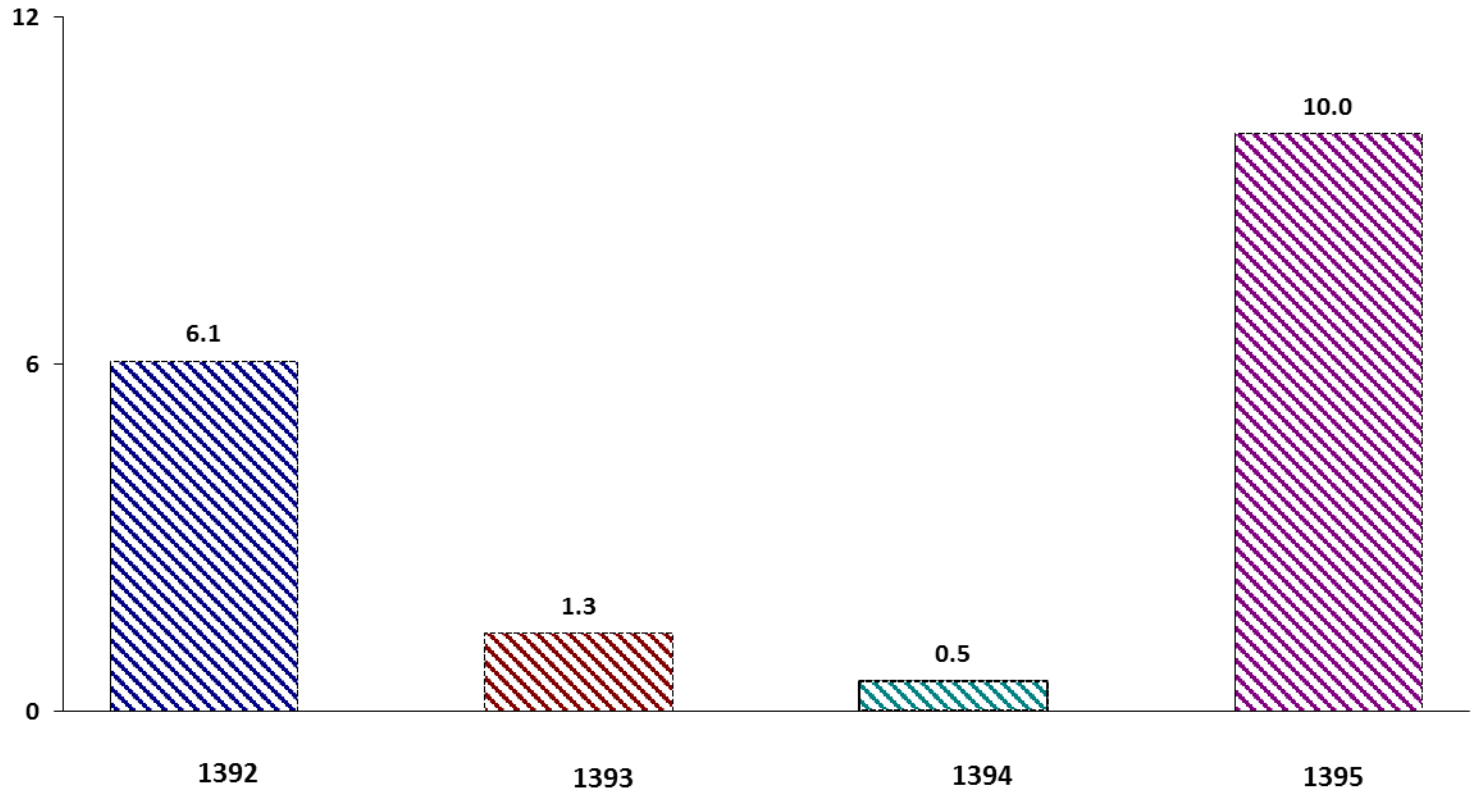
شیوع کلی ناهنجاری های مادرزادی دستگاه تناسلي و ادراري(در هر ده هزار تولد) درهرمزگان(95-1392)



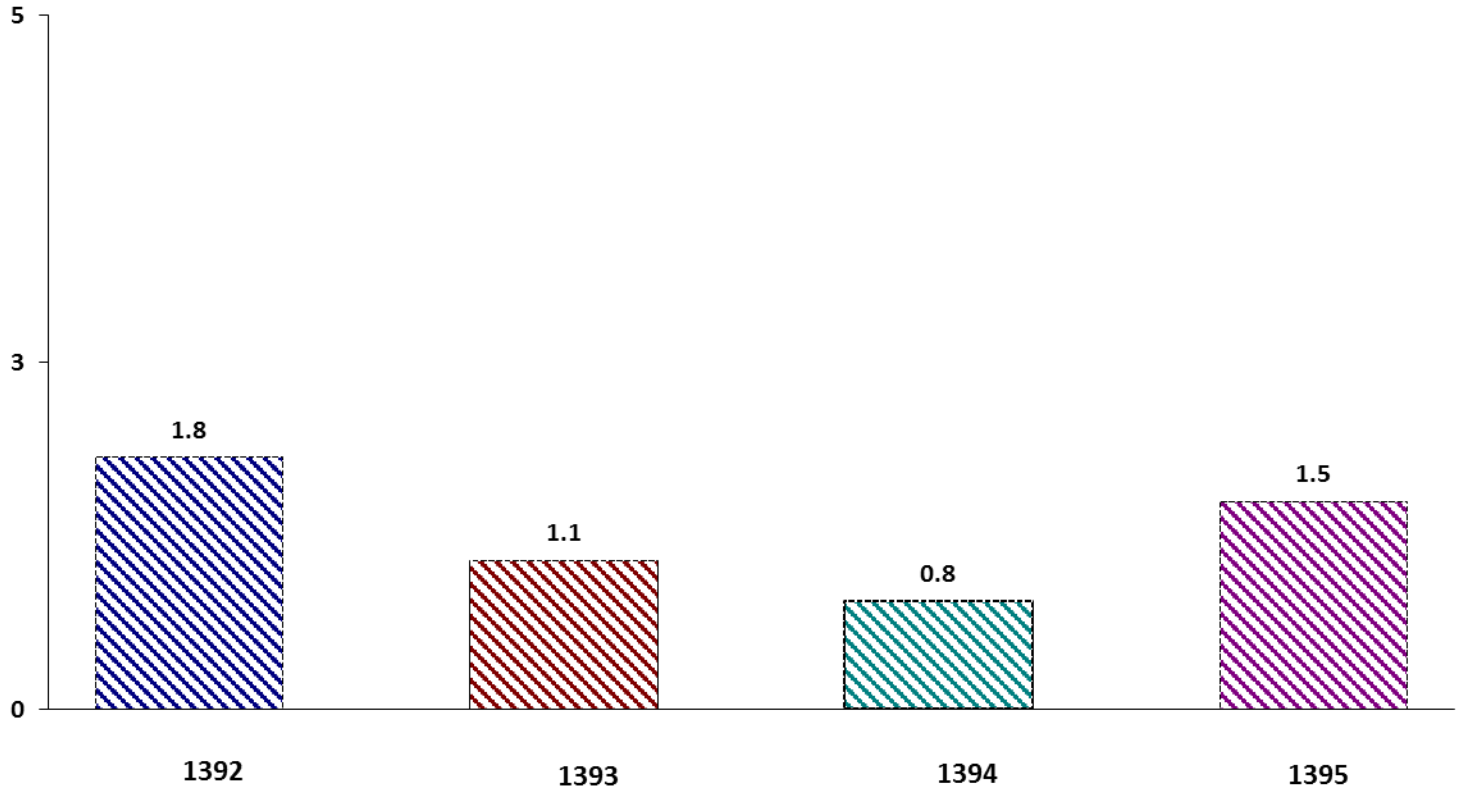
شیوع کلی ناهنجاری های مادرزادی کروموزومي(در هر ده هزار تولد) درهرمزگان(95-1392)



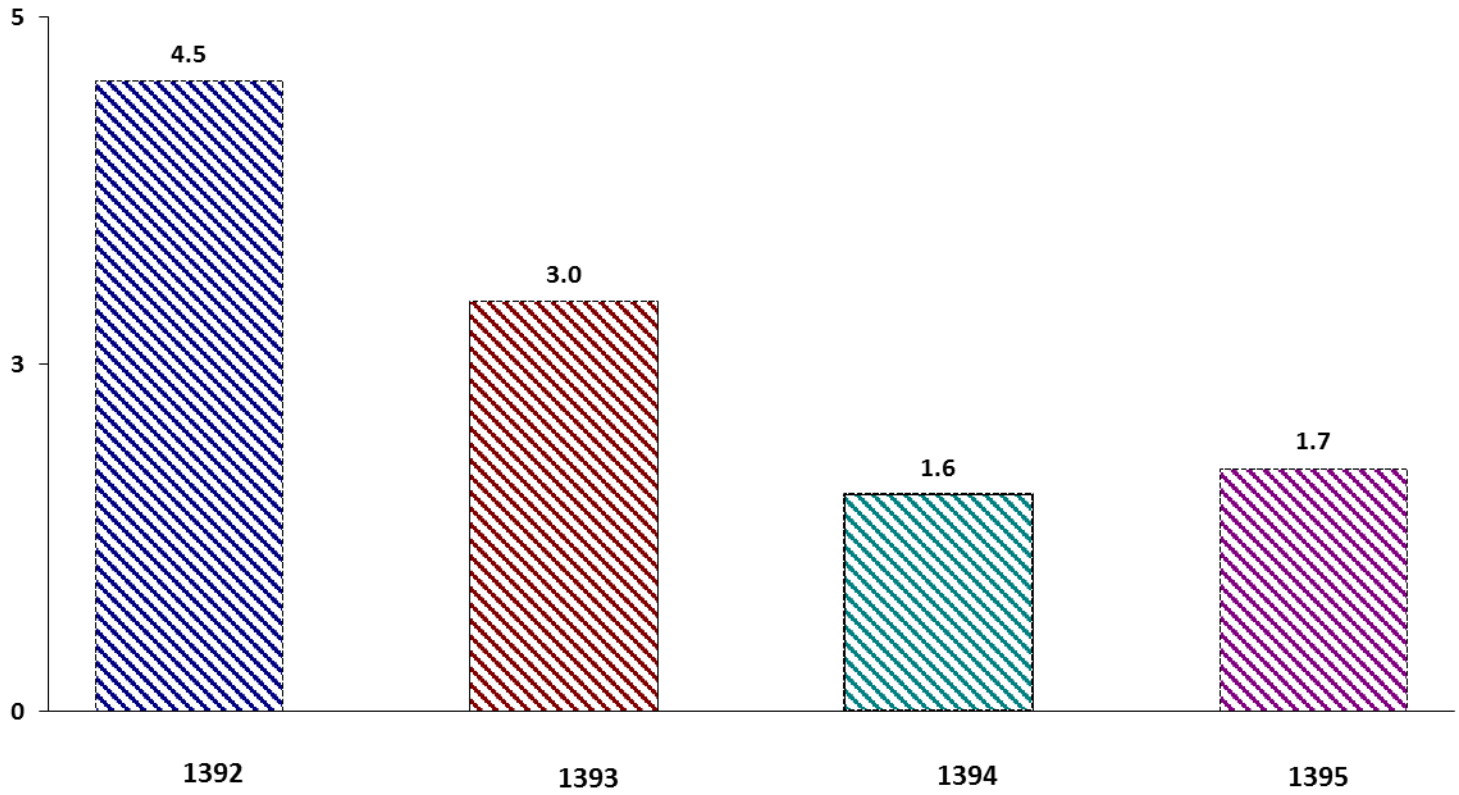
شیوع کلی ناهنجاری های مادرزادی عضلاني و اسکلتي(در هر ده هزار تولد) درهرمزگان(95-1392)



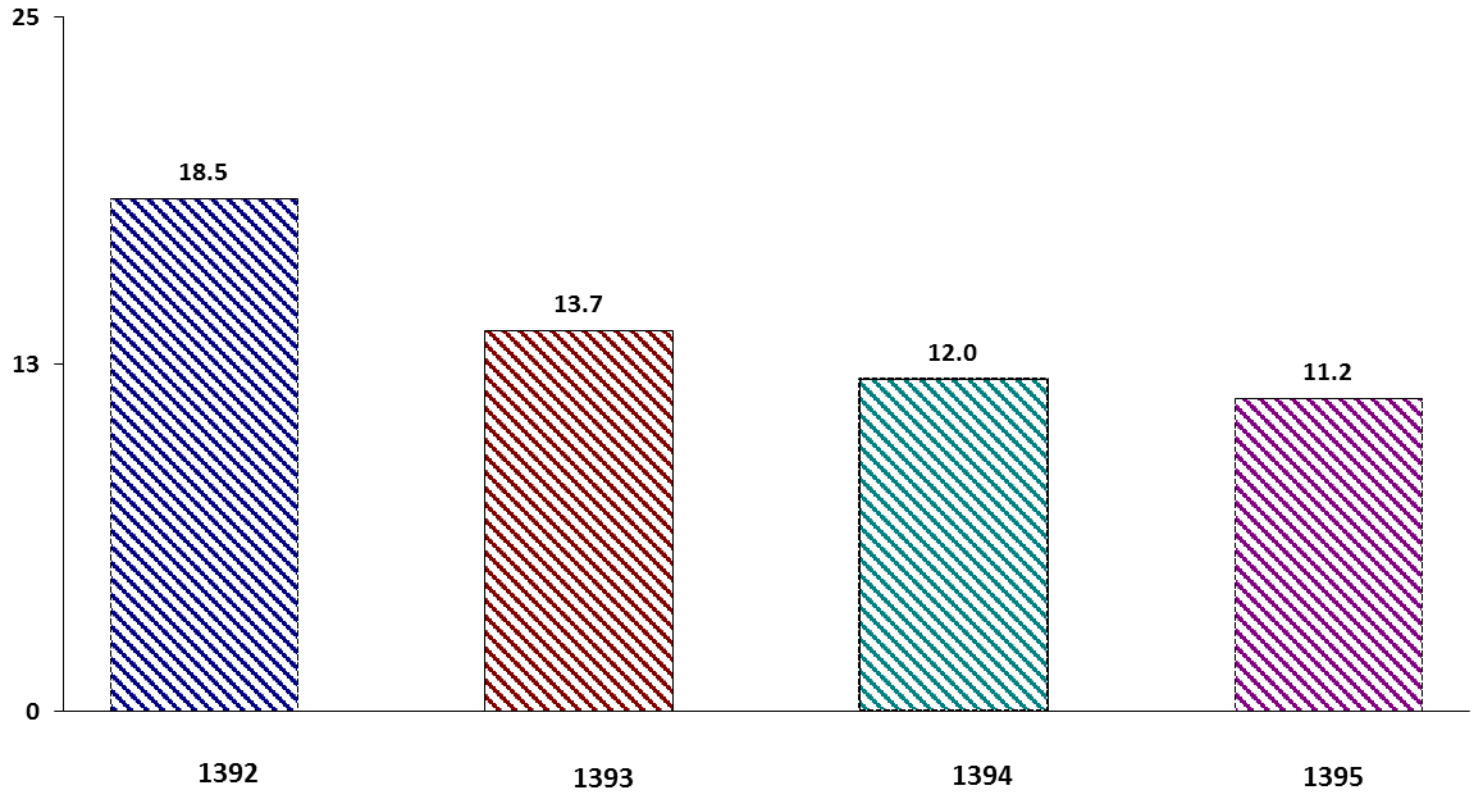
شیوع کلی ناهنجاری های مادرزادی قلبي(در هر ده هزار تولد) درهرمزگان(95-1392)



شیوع کلی ناهنجاری های مادرزادی گوارشي(در هر ده هزار تولد) درهرمزگان(95-1392)



شیوع کلی ناهنجاری های مادرزادی تعریف نشده(در هر ده هزار تولد) درهرمزگان(95-1392)



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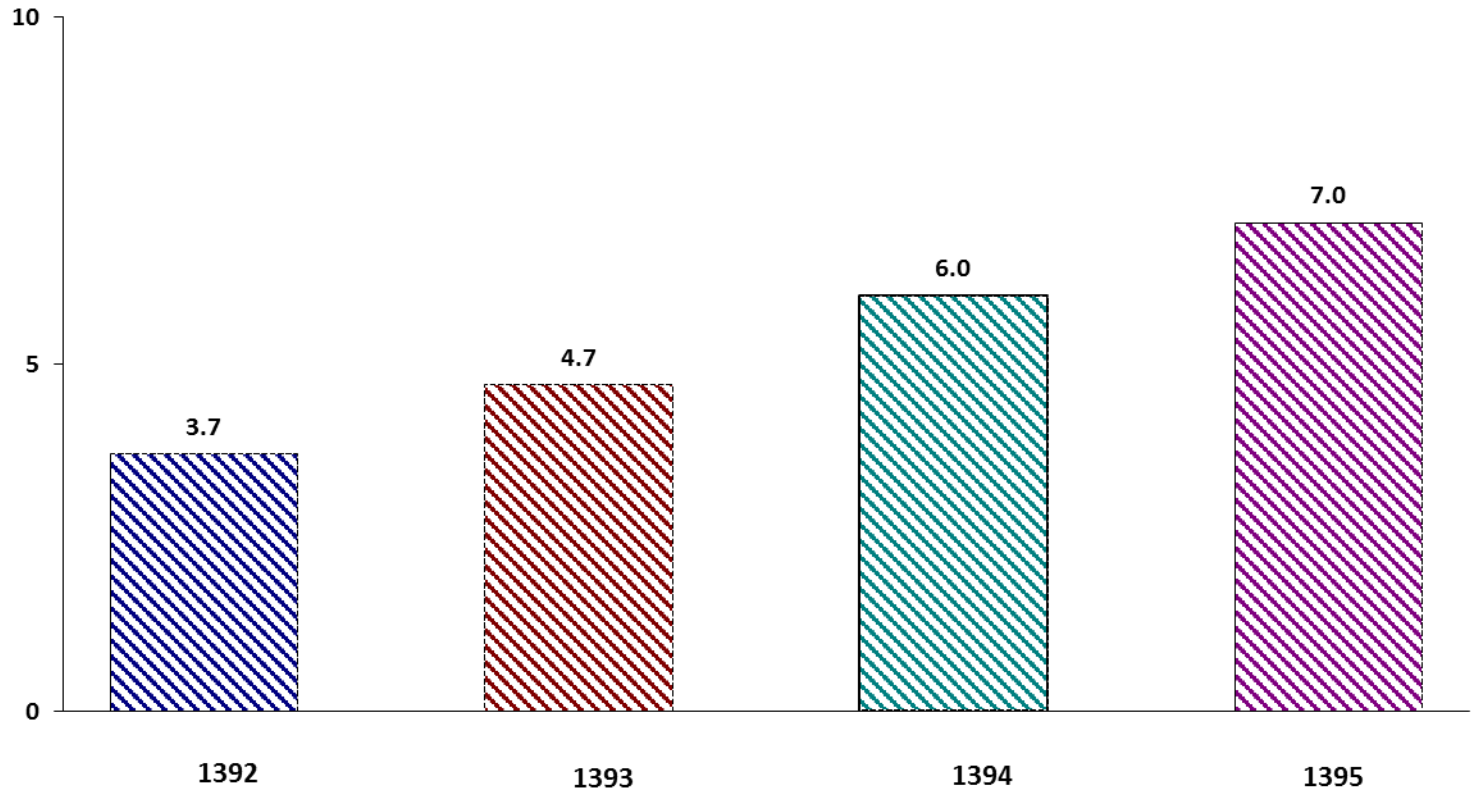

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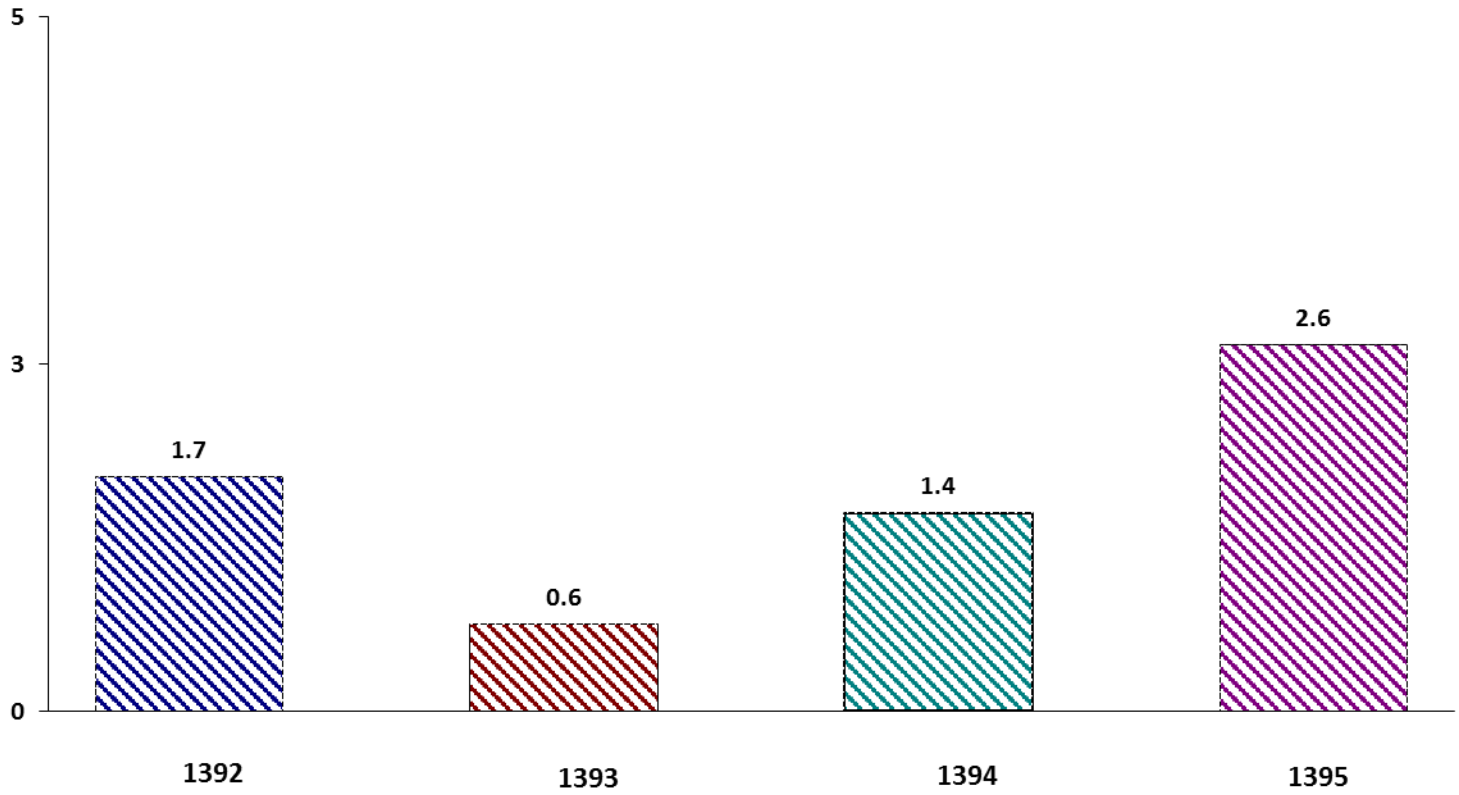

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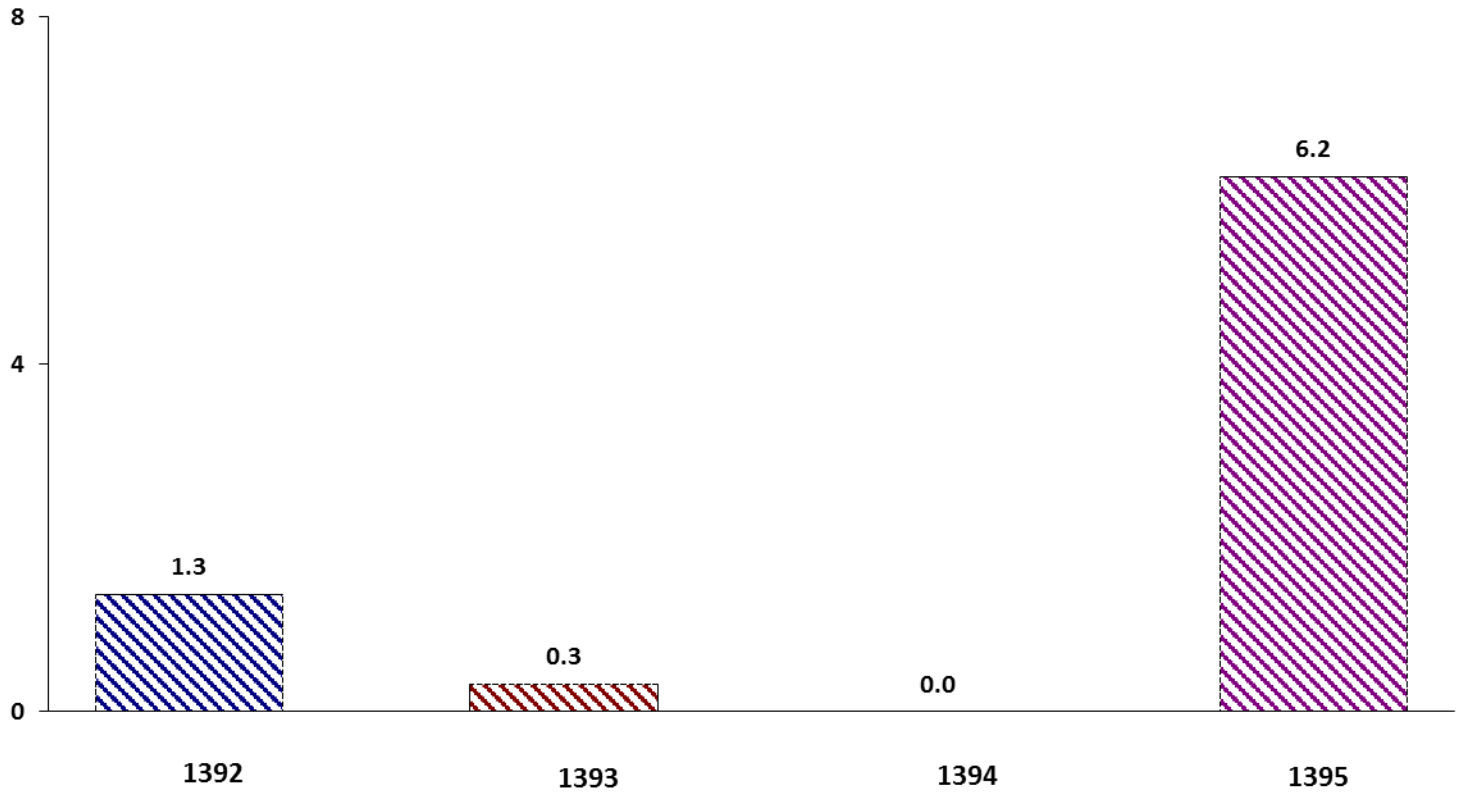

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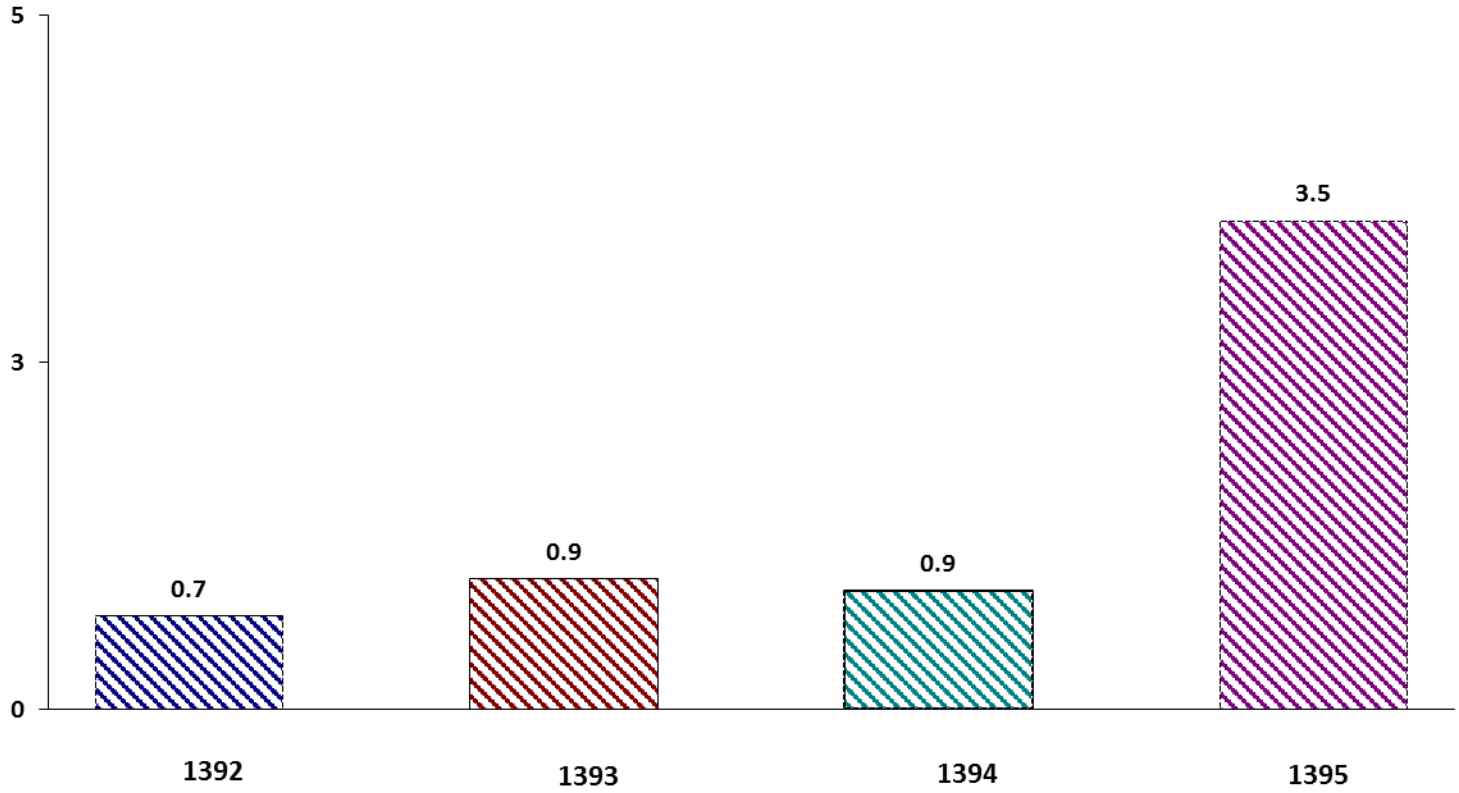

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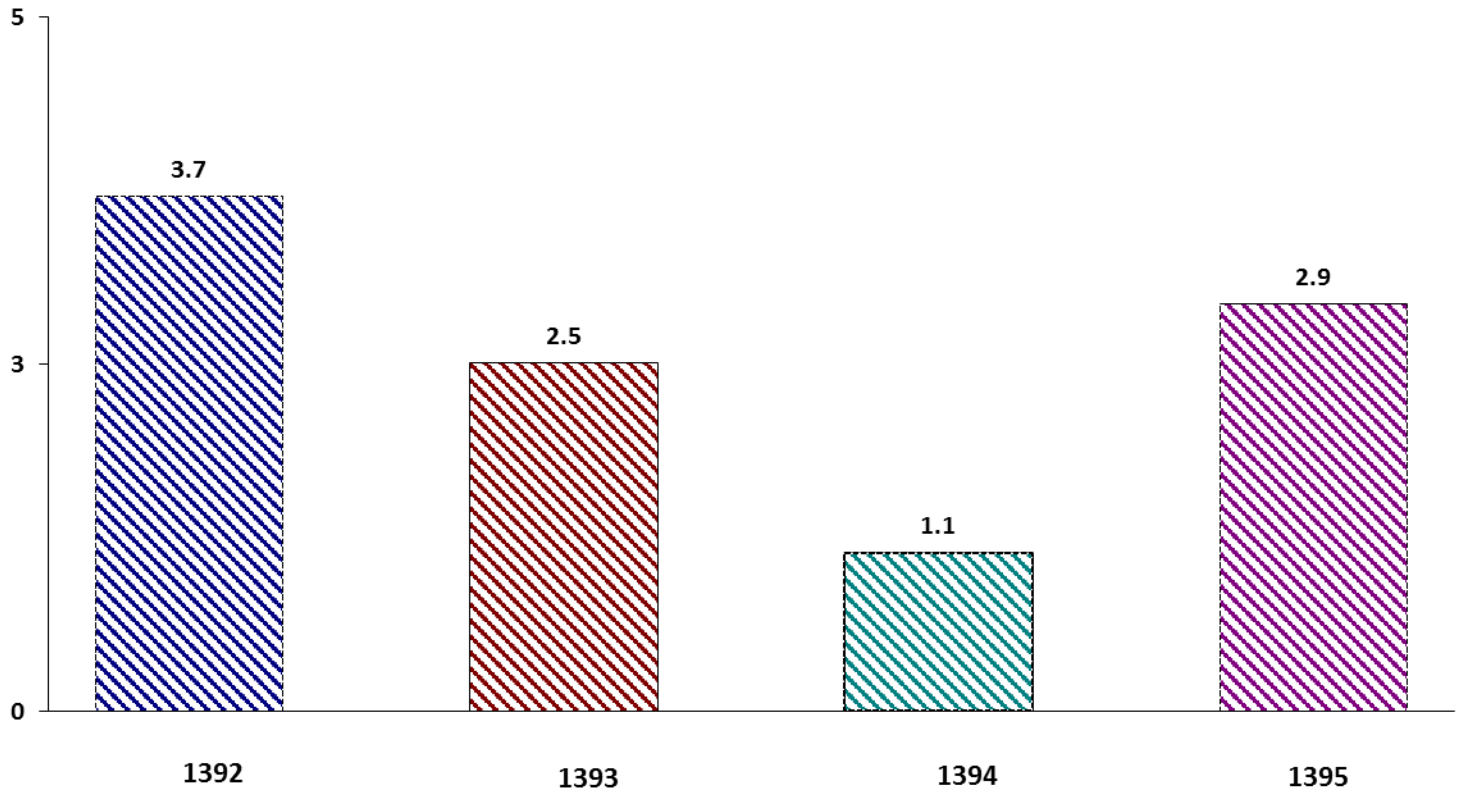

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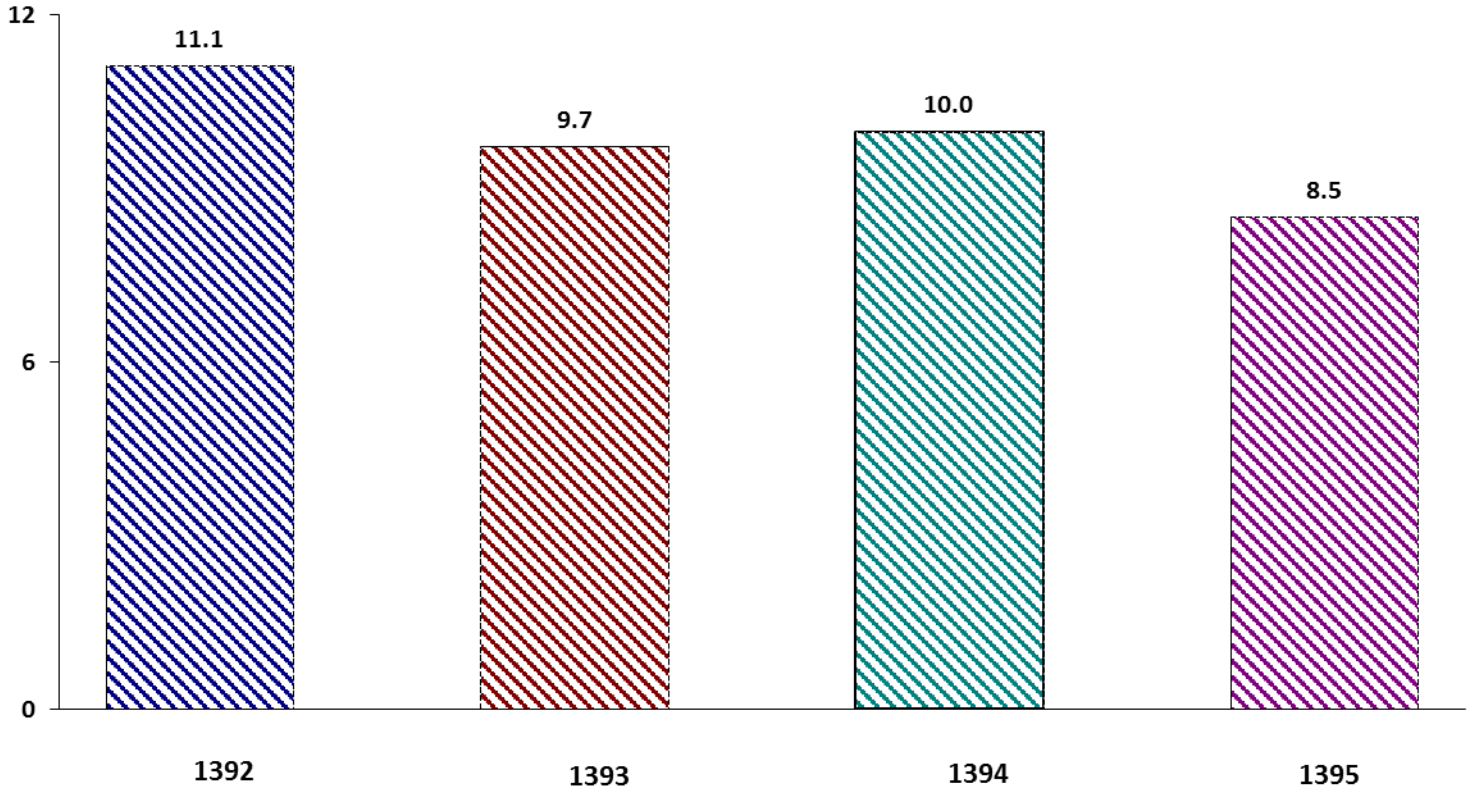

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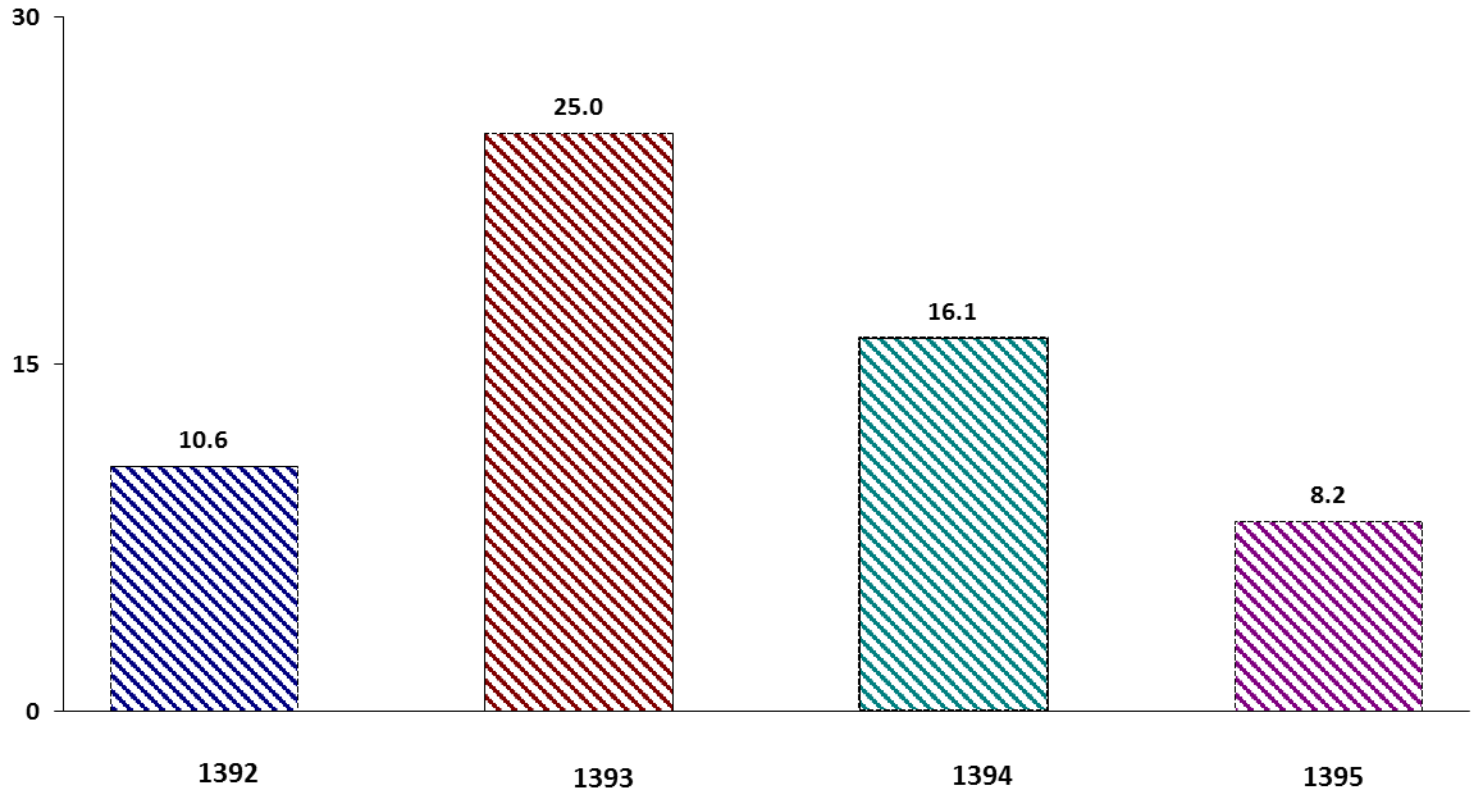

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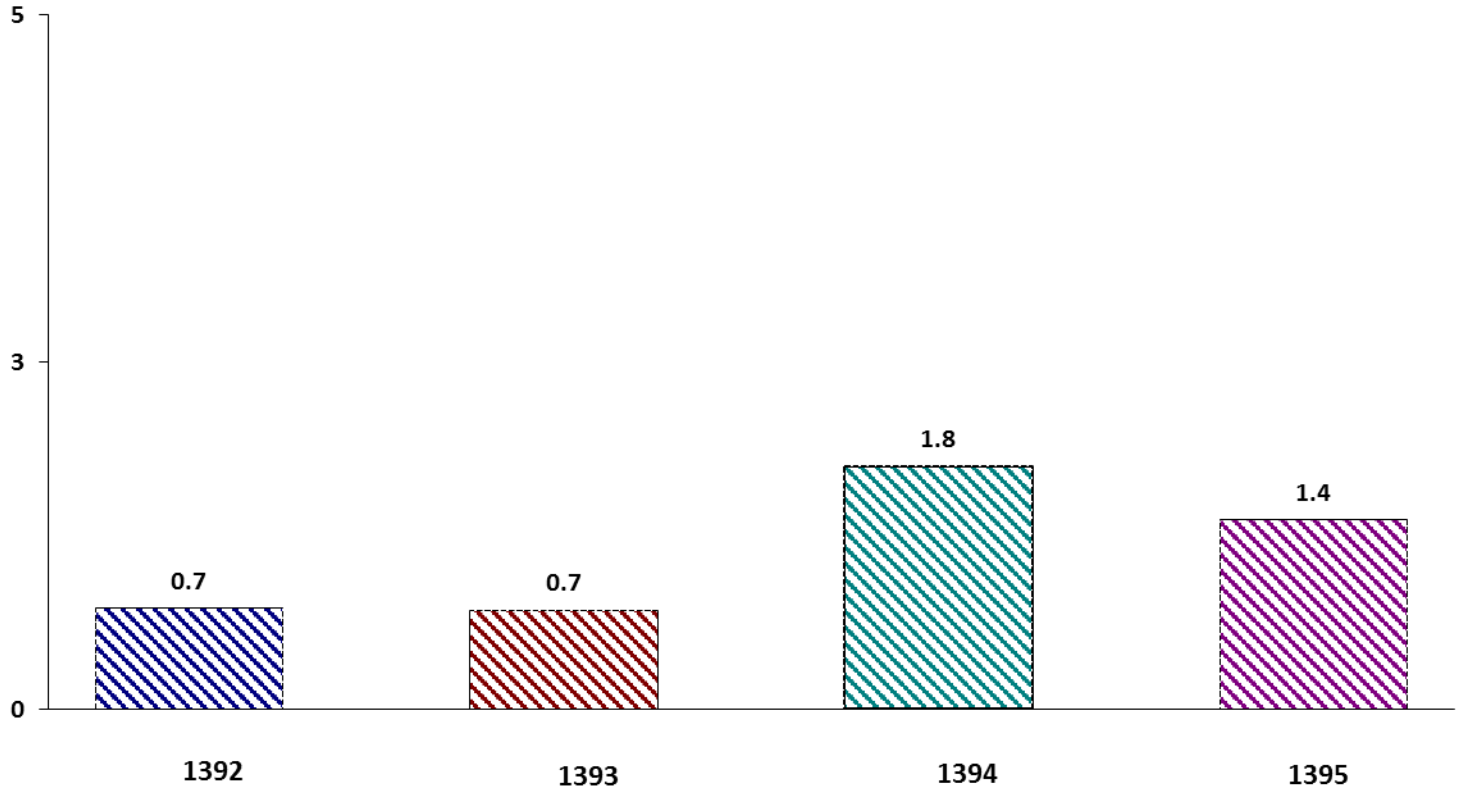

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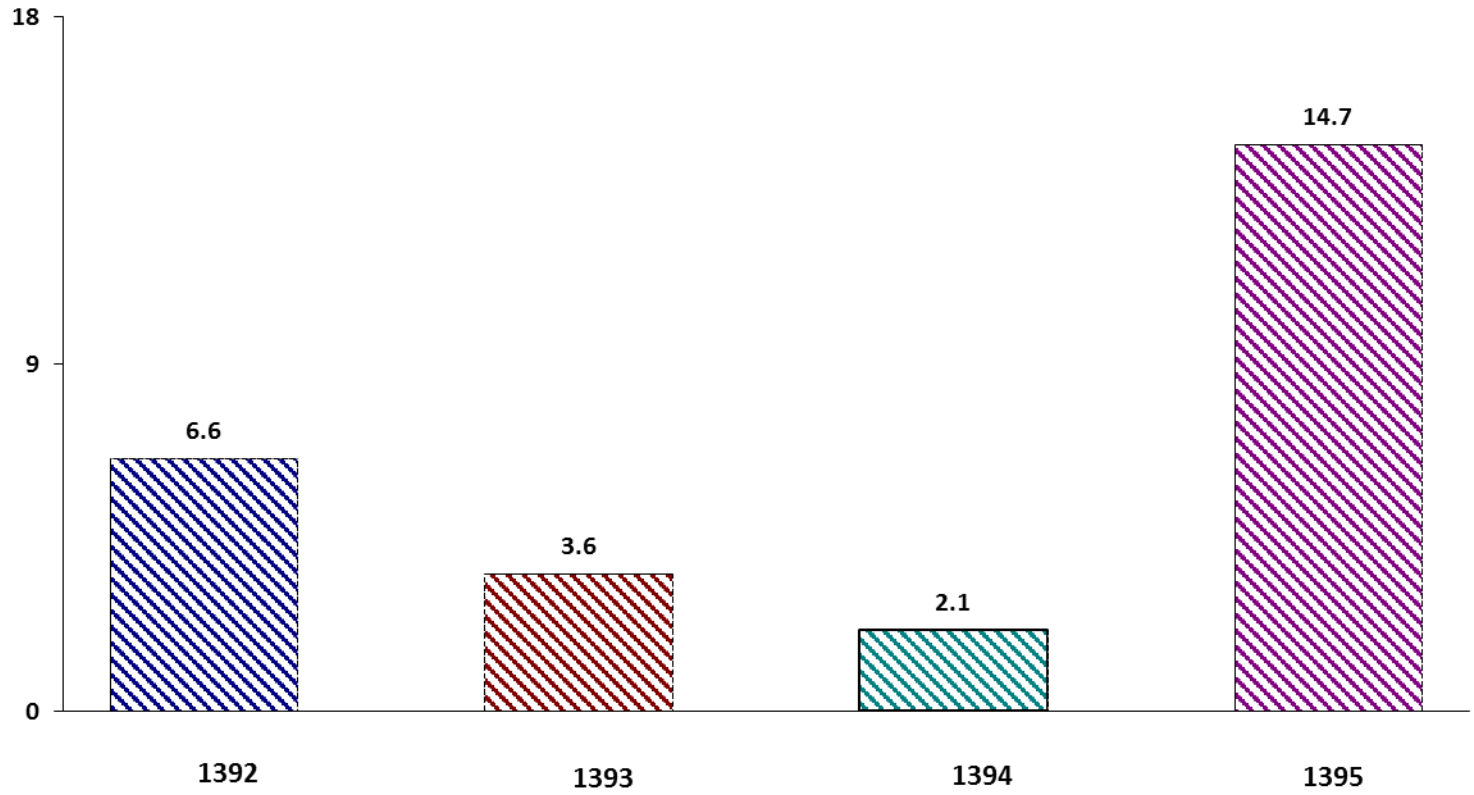

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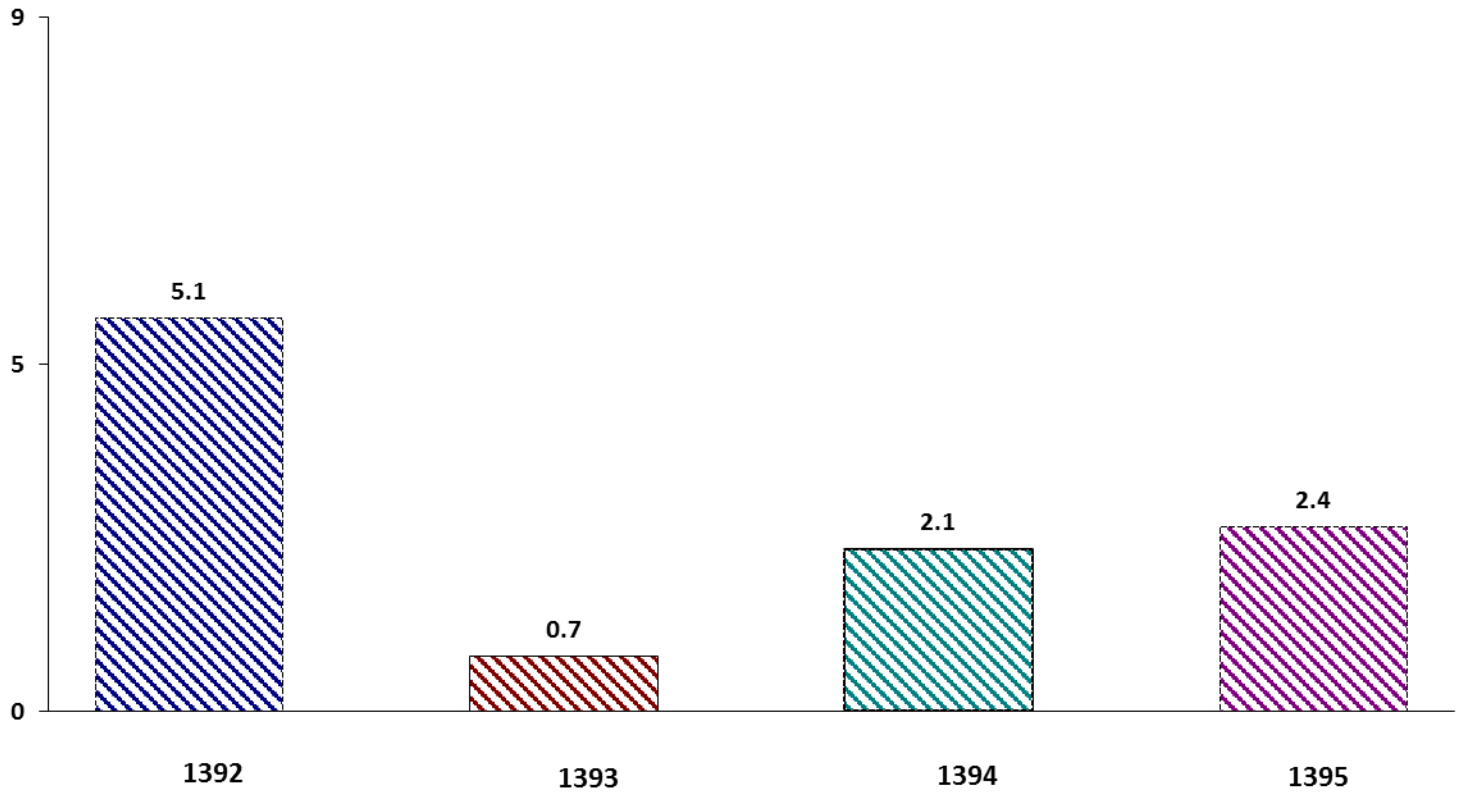

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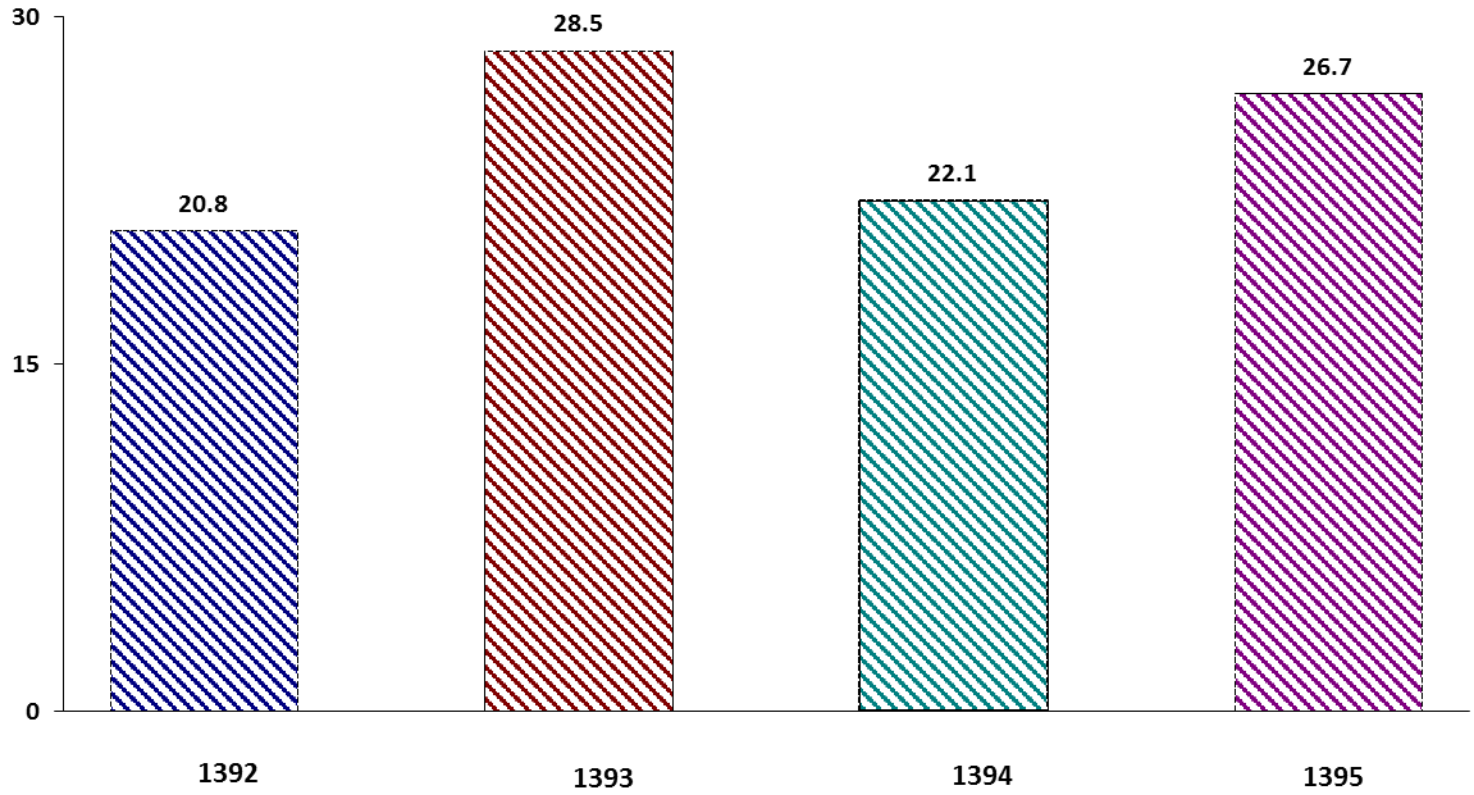


Preconception/Prenatal Family Health History Questionnaire

Today's date: _____ Person completing questionnaire: _____

	Patient	Partner/spouse
Name		
Date of birth		
Occupation		
Marital status (married, divorced, widowed, single)		
Last grade completed		
Height		
Weight		
Adopted	◯ Yes ◯ No	◯ Yes ◯ No

Past medical history (check all that apply)

	You	Partner	Explain checked items, include year or age
Surgeries	◯	◯	_____
Hospitalizations	◯	◯	_____
Major illnesses	◯	◯	_____
Chronic medical problems	◯	◯	_____
Allergies	◯	◯	_____
Learning problems	◯	◯	_____
Behavior problems	◯	◯	_____
Mental illness	◯	◯	_____

Ethnic Background

Where did your and your partner's ancestors come from before the United States? (check all that apply)

	You	Partner
Mediterranean (e.g., Italian, Greek)	◯	◯
European Caucasian (e.g., Irish, English, German)	◯	◯
African or African-American	◯	◯
Ashkenazi Jewish	◯	◯
Hispanic (e.g., Puerto Rican, Dominican, Mexican)	◯	◯
Cajun or French Canadian	◯	◯
Southeast Asian (e.g., Laotian, Chinese, Vietnamese)	◯	◯
Indian (from India)	◯	◯
Middle Eastern (e.g., Lebanese, Iranian, Egyptian)	◯	◯
Native American	◯	◯
Other _____	◯	◯

Preconception/Prenatal Family Health History Questionnaire

march of dimes

Date of first day of last menstrual period _____
Your age _____ If pregnant: your age at delivery _____ Current age of partner _____

Do you:
(if pregnant, also include all exposures since last menstrual period)

	Yes	No
Take any medications (prescription or non-prescription)?	◯	◯
Take a daily multivitamin or folic acid supplement?	◯	◯
Drink alcohol (beer, wine, hard liquor)?	◯	◯
Smoke cigarettes?	◯	◯
Use any recreational drugs (cocaine, marijuana, heroin)?	◯	◯

For any "**yes**" answers, describe below, including amounts and dates, if known.

_____

_____

Have you had:	**Yes**	**No**	**Have you been exposed to:**	**Yes**	**No**
Chicken pox (varicella)	◯	◯	Radiation (X-rays)	◯	◯
Fifth disease (parvovirus)	◯	◯	Chemicals (e.g., organic solvents, mercury)	◯	◯
Cytomegalovirus	◯	◯			
Toxoplasmosis	◯	◯	Raw meat (e.g., eaten steak tartar)	◯	◯

For any "**yes**" answers, describe below, including dates and details, if known.

_____

_____

_____

Did your mother take a medication called
"DES" while pregnant with you? ◯ **Yes** ◯ **No** ◯ **I do not know**
Were you born preterm? ◯ **Yes** ◯ **No** ◯ **I do not know** If so, how early? _____weeks

Do you have a personal history of:	**Yes**	**No**
Thyroid disease	◯	◯
Diabetes	◯	◯
Seizures	◯	◯
Hyperphe or phenylketonuria (PKU)	◯	◯
Deep vein thrombosis	◯	◯
Lupus	◯	◯
Other chronic conditions:	◯	◯

_____

Please list total number of prior:

Pregnancies	_____
Full-term births	_____
Multiple gestation pregnancies (e.g., twins)	_____
Preterm births (<37 wks)	_____
Preterm labor (<37 wks)	_____
Stillbirths	_____
Miscarriages (<24 wks)	_____
Elective abortions	_____
Living children	_____

Preconception/Prenatal Family Health History Questionnaire

For the questions below, please check the boxes for those conditions that have occurred in your or your partner's/ spouse's families. Include yourself AND your spouse/partner, as well as your and his siblings (full and half), parents, children, grandparents, aunts, uncles, nieces, nephews and first cousins, if possible.

	Your Family	**Partner's Family**	**Who is affected?** (you, parent, sib, etc.)
Anencephaly or spina bifida (openings in the skull or spine)	◯	◯	_____
Hydrocephalus (water on the brain)	◯	◯	_____
A large, small or unusually shaped head	◯	◯	_____
Blindness or other vision problems	◯	◯	_____
Cataracts	◯	◯	_____
Glaucoma	◯	◯	_____
Deafness or significant hearing loss	◯	◯	_____
Unusual shape, size or position of ears	◯	◯	_____
Cleft lip and/or cleft palate (opening in lip and/or roof of the mouth)	◯	◯	_____
Dental problems (missing, extra or abnormally formed teeth)	◯	◯	_____
Speech problems	◯	◯	_____
Congenital heart defect (e.g., "hole" in the heart)	◯	◯	_____
Heart attack or coronary artery disease	◯	◯	_____
Respiratory disease or chronic lung condition	◯	◯	_____
Asthma	◯	◯	_____
Allergies	◯	◯	_____
Cystic fibrosis	◯	◯	_____
Alpha-1-antitrypsin deficiency	◯	◯	_____
Pyloric stenosis	◯	◯	_____
Birth defects of the bowels or intestines	◯	◯	_____
Kidney problems	◯	◯	_____
Polycystic kidneys, missing or extra kidneys	◯	◯	_____
Genital or urinary tract defects	◯	◯	_____
Congenital hip dislocation (born with dislocated hips)	◯	◯	_____
A birth defect of an arm or a leg	◯	◯	_____
Unusually formed bones or many broken bones	◯	◯	_____
Scoliosis (curved spine)	◯	◯	_____

Preconception/Prenatal Family Health History Questionnaire

	Your Family	Partner's Family	Who is affected? (you, parent, sib, etc.)
Unusually formed hands or feet (including club foot)	◯	◯	
Very short or tall stature	◯	◯	
Dwarfism	◯	◯	
Marfan syndrome	◯	◯	
Muscle weakness or poor coordination	◯	◯	
Muscular dystrophy	◯	◯	
Mental retardation or developmental delay	◯	◯	
Learning disabilities or a slow learner	◯	◯	
Attention deficit or hyperactivity	◯	◯	
Autism	◯	◯	
Seizures, epilepsy or convulsions	◯	◯	
Down syndrome or other chromosome syndrome	◯	◯	
Fragile X syndrome	◯	◯	
Tay-Sachs disease	◯	◯	
Canavan disease	◯	◯	
Phenylketonuria (PKU)	◯	◯	
Gaucher disease	◯	◯	
Alzheimer's disease or other form of dementia	◯	◯	
Huntington's disease	◯	◯	
Neurofibromatosis	◯	◯	
Schizophrenia or other mental illness	◯	◯	
Manic depression (bipolar)	◯	◯	
Unipolar disorder (severe depression)	◯	◯	
Birthmarks or unusual growths on skin	◯	◯	
A chronic skin condition (e.g., eczema)	◯	◯	
Patches of different colored hair	◯	◯	
Patches of different colored skin	◯	◯	
Bleeding or clotting disorder (e.g., hemophilia)	◯	◯	
Hereditary anemia (e.g., thalassemia, sickle cell, other)	◯	◯	
Deep vein thrombosis	◯	◯	
Factor V Leiden	◯	◯	
High cholesterol	◯	◯	
Stroke	◯	◯	
Hemochromatosis (iron storage condition)	◯	◯	

Preconception/Prenatal Family Health History Questionnaire

	Your Family	Partner's Family	Who is affected? (you, parent, sib, etc.)
Diabetes	◯	◯	_____
Thyroid disease	◯	◯	_____
High blood pressure or hypertension	◯	◯	_____
Breast cancer	◯	◯	_____
Ovarian cancer	◯	◯	_____
Colon cancer	◯	◯	_____
Other cancers or tumors	◯	◯	_____
Born preterm (<37 weeks)	◯	◯	_____
Stillbirths	◯	◯	_____
Infant or childhood deaths	◯	◯	_____
Two or more miscarriages or pregnancy losses (in the same person)	◯	◯	_____
Infertility or sterility (unable to get pregnant or have children)	◯	◯	_____
Premature ovarian failure (early menopause)	◯	◯	_____
Primary amenorrhea (never had a period)	◯	◯	_____

Have you, your partner/spouse, or anyone in your family had genetic testing? ◯ **Yes** ◯ **No**
If yes, please explain:

_____

_____

Are you and your partner/spouse related as first cousins or in any other way as blood relatives? ◯ **Yes** ◯ **No**
If yes, please explain:

_____

_____

For office use only

Significant findings:

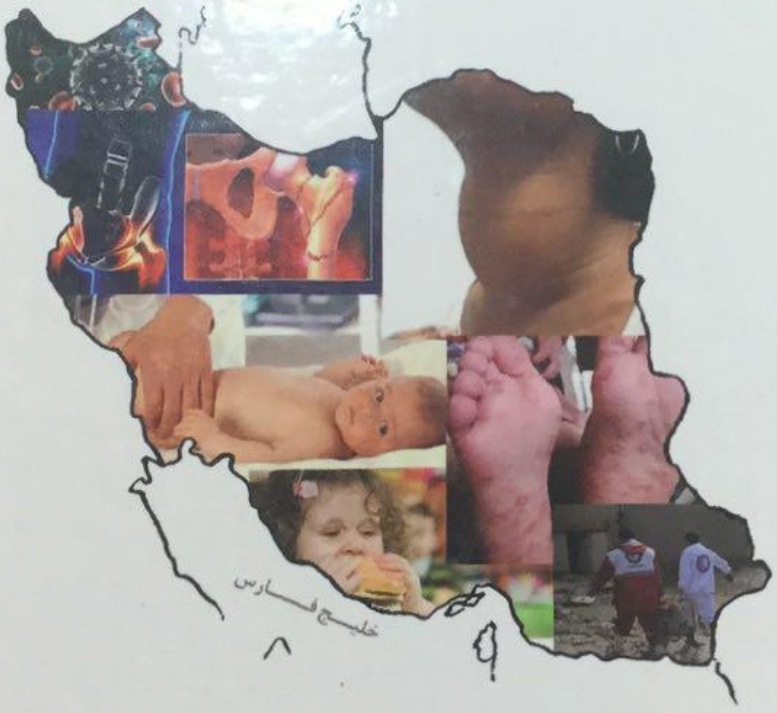
Recommendations:

Date discussed with patient/family _____HCP name/initials _____

Patient/parent/guardian signature X_____

اپیدمیولوژی و کنترل بیماری‌های شایع در ایران

ویراست چهارم



دکتر فریدون عزیزی

دکتر حسین حاتمی دکتر محسن جانقربانی

پژوهشکده علوم غدد درون ریز و متابولیسم
دانشگاه علوم پزشکی و خدمات بهداشتی- درمانی شهید بهشتی

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Original Article

Defining a Core Data Set for Registry of Esophageal Atresia in the Northwest of Iran

Kamran Saeedkhani[a]; Leila R. Kalankesh[a]; Saeed Dastgiri[a]; Mandana Rafeey[a]

Abstract: Background: Defining the core data set is the main step for establishing a registry system. The aim of this study was to define the core data set for the registry of esophageal atresia in the northwest of Iran. Methods: First, the preliminary list of data elements was extracted from the related registries of other countries, as well as from the literature. Then, a group of multidisciplinary experts was asked to score the tabulated list of data elements in terms of their importance using a 5-point Likert scale through a dual-round Delphi technique. Availability of data was assessed through a medical record review of 410 patients with esophageal atresia who had been hospitalized between March 2006 and March 2016 in Tabriz Children's Hospital. Results: The main classes of data were defined, including maternal information, patient demographics, clinical information, complications, and follow-up data. Thirty-two of 51 data elements (the core data elements) had 100% availability. Demographic data were completely available for 60% of the data elements. For clinical data, the availability rate was above 75%, while for complications and follow-up, it was 100% (except for the weight and height). In the category of maternal data, no data was available on the genetic screening and amniocentesis. Conclusion: This study presents the core data set required for establishing an esophageal atresia registry in the northwest of Iran. A considerable number of identified cases and high availability of patient data indicated the feasibility of establishing the first esophageal atresia registry in the area.

Key words: *core data set, esophageal atresia, registry*

Introduction

Esophageal atresia is a rare malformation of the digestive system in which the esophagus does not develop normally. It causes the esophagus to end in a blind-ended pouch rather than connecting to the stomach. It affects one in 2,500–4,500 live births, with males having a slightly increased incidence. In 86% of cases, there is a fistula between the esophagus and trachea. There is no fistula in 7% of cases, while 4% of the fistula is without the atresia. The prenatal diagnosis of esophageal atresia is possible in a very low proportion of the cases. This anomaly is diagnosed either before or at the time of birth. Patient survival mainly depends on the surgical operation during the first days after birth.[1-3]

About 50% of patients with esophageal atresia have additional anatomic malformations. Defects have been reported in the cardiovascular (35%), gastrointestinal (24%), genitourinary (24%), musculoskeletal (13%), and central nervous (10%) systems. Thirty six percent of cases are marked by additional anomalies from the VACTERL spectrum (vertebral anomalies, anorectal atresia, congenital heart malformations, tracheoesophageal fistula, renal abnormalities, and limb defects) or CHARGE syndrome (coloboma, heart defects, atresia choanae, retardation of growth and/or development, genital hypoplasia, and ear deformities).[4]

While the etiology of esophageal atresia is unknown, there are reports on the role of different environmental factors in this malformation.[5] Evidence also shows the ethnic and temporal trend of the esophageal atresia.[2] A study conducted in 5 different regions of the United Kingdom estimated the prevalence of esophageal atresia to range from 0.7–3.2 per 10,000 births. A similar variation in the prevalence estimates has been reported across the Americas. For instance, the prevalence rates for Hawaii, Texas, and California were 2.34, 2.33, and 2.83(per 10,000 births), respectively. In European countries, Iceland has a prevalence rate of 1.83 while Strasburg in France and the northern region of the United Kingdom showed rates of 2.96 and 3.13 (per 10,000 births), respectively. The lowest rate has been reported in Spanish and African communities.[2] The prevalence of esophageal atresia also varies in different areas of Russia, with an average estimate of 2.03 (per 10,000 births).[6]

The scarcity of data on rare diseases such as esophageal atresia—including prevalence, management, and outcome data—is an issue. The prevalence of esophageal atresia is usually calculated using the data from the global network of malformation registries worldwide. Due to the general focus of the network on several congenital anomalies and malformations, it lacks precise and detailed information about esophageal atresia, including its early and late outcomes. A dedicated registry for esophageal atresia could provide important scientific information about outcomes. A registry could also be used as a source of epidemiological data for making related health care policies. Moreover, data obtained from such a registry would be essential for evaluating and revising existing guidelines on the management of esophageal atresia.[7-9]

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This research has been approved by the ethics committee of Tabriz University of Medical Sciences.

A core data set is necessary to establish both paper-based and electronic registries.[10] So far, core data sets for congenital anomalies,[11,12] cystic fibrosis, [13] and 70 other diseases have been developed in Iran for establishing registries.[14] To date, to the best of our knowledge, no research has been conducted on developing a core data set or registry system for esophageal atresia in Iran. This paper presents the first attempt to define a core data set for establishing a registry system of esophageal atresia in the northwest region of Iran.

Methods

To extract a list of data elements, the researchers carried out a literature review on the esophagus atresia registry and cohorts. Among the main sources were the National Esophageal Atresia Epidemiologic Registry,[8] the Turkish Esophageal Atresia Registry,[15] the Federation of Esophageal Atresia and Tracheoesophageal Atresia,[16] the International Network of Esophageal Atresia,[17] and the Belgian Esophageal Atresia Study,[18] as well as the database of 371 patients treated for esophageal atresia at the Pediatric Surgical Center of Amsterdam between 1947 to 2000 in the Netherlands.[19] A preliminary list of data elements was assembled based on the information extracted from the literature. First, a tabulated list of data elements was prepared. Then, 2 rounds of Delphi techniques were conducted. The Delphi method has been defined as the multistage survey attempting to achieve consensus on an issue. In fact, this technique is used to obtain a collective view from experts where their opinion is important. The Delphi process consists of 2 or more rounds of a questionnaire administered to an expert panel.[20] At the first round, the multidisciplinary experts (including pediatricians, pediatric gastroenterologists, and epidemiologists) were asked to score the tabulated list of data elements in terms of their importance by using a 5-point Likert scale (ranging from 1–5).

Data elements were accepted for inclusion into the minimum data set if they were scored a 4 or 5 by at least 51% of the experts. If at least 51% of the experts scored data items as 1 or 2, those elements were discarded from the data set. Data elements that obtained a score between 2 and 4 were assessed in the second round of Delphi. Data elements suggested by the experts in the first round also went through the second round of Delphi. When scored 4 or 5 by more than 50% of the experts, they were added to the minimum data set; otherwise, they were discarded from the final list.

In the second phase of the study, the researchers evaluated the data availability of the minimum data set defined in the previous stage through reviewing the medical records of 410 patients hospitalized with a diagnosis of esophageal atresia in Tabriz Children's Hospital from 2006–2016. This center is the main pediatrics specialty referral hospital in the northwest of Iran.

Results

Identification of Initial Data Elements

Overall, 4 classes of data (54 data items) were identified from the related literature and existing esophageal registry systems. The data categories include maternal information, patient demographics, clinical information, complications, and follow-up data. Overall, 34 data elements were determined as the final data set:

- *Demographics:* first name, surname, father's name, national identification number, sex, date of birth, ethnicity, weight at birth, height at birth, type of residence, address of residence (including province, city, suburb, and telephone number), hospital admission, birth order, parental consanguinity of, and number of births (singleton vs multiple)
- *Clinical data:* gestational age at birth, delivery mode, family history of congenital anomalies, Apgar score at birth, neonate blood group, diagnosis time of esophageal atresia, type of esophageal atresia, *International Classification of Diseases* (ICD)-10 code for type of esophageal atresia, comorbid congenital anomalies, ICD-10 codes for comorbid congenital anomalies, surgical procedure type, surgical procedure code, reoperation during first hospitalization, discharge type, discharge disposition, and cause and date of death (if applicable)
- *Complications and follow-up:* hospital readmission, weight at the readmission, readmission date, height at readmission, cause of the readmission, ICD-10 code for the cause of readmission, type of therapeutic procedure during the readmission, type of surgical procedure during readmission, and code for the surgical procedure during readmission
- *Maternal data:* mother's date of birth, genetic screening during pregnancy, amniocentesis, and polyhydramnios

Table 1 illustrates the availability of the final data set in the real world based on reviewing the charts from 410 patients in a pediatric hospital during the 10-year period (2006–2016).

As shown in the Table 1, 14 of 24 data elements in the demographic category had 100% availability. The name could be found in 80% of the records. Only 1 data element (landline phone number) in this class had availability below 50%.

For clinical data, 12 of 16 data items had availability of 100%. Two data elements in the category of complications were completely unavailable, while other elements in this class had 100% availability. In the category of maternal data, maternal age and mother national code were available in 100% and 56% of the cases, respectively. Data on conducting a genetic test as well as amniocentesis in this class of data were not available.

Discussion

This work presents the very first effort undertaken for developing the core data set for registry of esophageal atresia in the northwest region of Iran. Establishing a core data set is not a new concept. A core data set is of great importance, as it can be used for sustainability of the care

Table 1. Percentage of the Availability of the Data Elements for a Patient with Esophageal Stresia (2006–2016)

Class	*Data Element*	*%*
Demographic data	First name	80
	Surname	100
	Father name	100
	Neonate national number	78
	Date of birth	100
	Hospital record number	100
	Gender	100
	Ethnicity	100
	Weight at birth	79
	Height at birth	73
	Province of residence	100
	City of residence	100
	Address	100
	Landline	47
	Mobile phone number	55
	Type of residence	100
	Admission date	100
	Discharge date	100
	Admission type	94
	Discharge type	100
	Discharge disposition	100
	Birth order	88
	Outcome of pregnancy(single vs multiple)	89
	Parental Consanguinity	58
Clinical data	Term vs preterm birth	100
	Gestational age at birth	100
	Mode of delivery	100
	Family history of congenital anomaly	59
	Apgar score (1–5 minute)	71
	Blood group	86
	Time of diagnosis	100
	Type of esophageal atresia	100
	Diagnosis code	100
	Comorbid congenital anomalies	100
	Date of surgical procedure	100
	Type of surgical procedure	100
	Surgical procedure code	100
	Reoperation during the first hospitalization	100
	Polyhydramnios	17
	Readmission	100
Complications and follow-ups	Date of readmission	100
	Weight at readmission	0
	Height at readmission	0
	Cause of readmission	100
	Code for cause of readmission	100
	Surgical procedure	100
	Code of surgical procedure	100
Maternal data	Mother national code	56
	Mother age	100
	Genetic screening	0
	Amniocentesis	0

on an individual level, for health care system evaluation on the organizational level, and for national and international comparison on the aggregated level.

Reviewing different studies carried out in esophageal atresia worldwide, as well as the existing registry systems, provided a basis for defining the core data set. The main classes of data were defined, including maternal information, patient demographics, clinical information, complications, and follow-up data. The data elements defined in this work were similar to the categories of data reported in the French registry system for esophageal atresia.[8] Some of the data items are also common with the etiological aspects of the esophageal atresia cohort in a study conducted in Sweden.[21] Some overlap can be seen between the present core data set with the elements reported in the epidemiological studies of esophageal atresia from Europe,[22] as well as data published from Hawaii[23] and Southwest of England.[24] The data elements defined in this project are also in accordance with variables used in 2 studies conducted on the complications of the esophageal atresia surgical repair in Iran.[25-27] They have a high similarity with the data elements deployed in the French[8] and Turkish registries of esophageal atresia.[15] These all imply the extent to which the core data set developed in this project can cover different purposes of the registry.

To make data comparable, ICD codes for diagnosis and procedures were included in the data set. This provides a mechanism for the standard definition of cases whether during casefinding or processing and reuse of the data. The use of ICD codes can increase the accuracy of identified cases.[28]

There are limited details about patients with esophageal atresia in the registry systems of congenital anomalies and information is scarce on treatment of the condition or its primary or late health outcomes. The improvements have happened during preoperative, postoperative, and intensive care of these patients. Survivors of esophageal atresia are reaching adulthood. Therefore, establishing the registry can facilitate continuity of care while transitioning care from childhood to adulthood.[29,30]

Some steps have been taken for developing population-based registry systems of esophageal atresia in some countries (eg, Australia and France).[8,31] Defining a necessary data set for registry of esophageal atresia can contribute to the quality of patient treatment, help clinicians provide

better health care services, and shed light on the evidence-based policymaking in this domain.

Reviewing the medical records of those with esophageal atresia revealed the availability of data in the real world. The statistics obtained on the availability of data elements are an indicator of high data feasibility for establishing an esophageal atresia registry system. Unavailability of some maternal data, such as genetic screening, amniocentesis, and diagnosis of cases before childbirth or polyhydramnios, can be attributed to the fact that this sort of data can mostly be found in maternal records residing in women-specialty hospitals or physician offices providing maternal care before childbirth.

Although esophageal atresia is among the rare congenital anomalies, a considerable number of patients with esophageal atresia were identified in this project. The number of cases identified (n = 410) is comparable with the number reported from the Netherlands between 1947 and 2000 (n = 371).[19] Moreover, the data elements were highly available in the patient charts. This means that establishing a registry of esophageal atresia in the northwest region of Iran is remarkably feasible. Considering patients with esophageal atresia need to receive care for a long period, the registry can facilitate the integration of patient information across the whole continuum of care and provide adequate information for conducting clinical research in the domain.

Findings on the availability of data in this study have been limited to a university pediatrics hospital in Tabriz, while other sources, including private hospitals and other centers, have not been investigated.

Conclusion

This study presents the core data set required for establishing the esophageal atresia registry in the northwest of Iran. A considerable number of the identified cases and high availability of patient data indicated that establishing the first esophageal atresia registry in the area is remarkably feasible.

Findings from this study provide baseline information and pave the way for establishing the registry of esophageal atresia. This may eventually facilitate research studies and help to implement preventive strategies in the community.

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From Covered Wagon to Tesla to Spaceship: A Personal History of Cancer Registration to Celebrate the 35th Year of Certification

Louise Schuman, MA, CTR

Covered Wagon

In 1979, I completed a certificate course in medical records technology to obtain what was then the accredited records technician (ART) certification, as I already had my bachelor's degree. Just before completing the course, I learned of cancer registry—then called *tumor registry*. Intrigued, I signed up for the tumor registry training program at the University of Southern California sponsored by the Los Angeles County population-based tumor registry. It was an 8-week course that met 2 days a week. On completion, I was lucky enough to get a job at a well-respected community hospital in my neighborhood, replacing a tumor registrar who was leaving. I took over as the only registrar and stayed for 10 and a half years. The following is a snapshot of what cancer registration was like "back in the day."

Then as it is it is now, the basic duty was abstracting. Medical records were all hard copies, and abstracting was done on an electric typewriter (does anybody still remember those?). We had to begin with case finding, which involved going through pathology reports daily and disease indexes monthly. The suspense file consisted of monthly folders with the path reports filed in alphabetical order and the disease index for that month, also in alphabetical order.

There was minimal coding and staging in 1979. The International Classification of Diseases for Oncology (ICD-O) 1 began in 1976. TNM classification began in 1977, effective for 1978 cases. However, the first real American Joint Committee on Cancer (AJCC) staging was for breast cancer in 1982. Summary stage was published in 1977 and was the most common form of staging for many years.

Once a case was abstracted, the form was placed in a folder for that site for that year in alphabetical order by patient last name, with deceased patients placed in the back of the folder, also in alphabetical order. In addition, each patient had a card typed with his or her name, primary site, and date of diagnosis, which was filed in a large file box in alphabetical order. This was called our *master patient index*. All patients were in the same file box, regardless of diagnosis or date of diagnosis. When a patient died, I placed a red dot on the card, but the card remained in the box.

Each patient also had a file card with the same information, but also including the patient address and phone number, as well as doctors' names and, most importantly, when the patient was last followed. This was called the *tickler file* and was filed in order by month according to when the patient was required to be followed. When a patient died, his or her card was removed from the box.

Interestingly, the medical records department had a computer system to keep track of patients. Each month, I would use one of the department computers to look for patients who had been readmitted, much as we do now. Fortunately for me, the medical record department was very close to administration. The senior vice president would pass by often and see me at this computer. One day, after months of seeing me at that computer, he said he would give it to me because he was hardly using it. This must have been sometime in 1980. Unbelievable, but true. At one point, the information technology (IT) department decided that maybe I should have software to do my work rather than using a typewriter. They sent a young man who was fresh out of school, I believe, to write me a program in a week. He shadowed me for a week watching me abstract and attend meetings. He went back to the IT department and said that it would take him at least 6 months to write a program. That ended that.

Finally, we had the accession register, which was usually an actual ledger book—one for each year. As a patient was abstracted, he or she was assigned an accession and sequence number. There was an elaborate way of counting a double primary abstracted at the same time or even in another year. This was so that we could keep an accurate count of the number of patients entered into our "database" annually.

To do a study or, more likely, prepare an annual report (which was a requirement then), I had to pull all the abstracts for the site under study, often for multiple years. Each patient abstract had to be manually counted for whatever parameter was being studied. We always had to do a survival study. If it were for breast cancer, for example, it could involve 100 to 150 patients. Our annual caseload then, if I remember correctly, was about 350 to 400 cases. Naturally, my first count was usually 1 or 2 patients off, meaning I had to count and recount. It usually took about a month to complete my part of the annual report.

Preparing for a Commission on Cancer (CoC) survey involved filling a binder for each standard with proof that we met the requirements for each standard. The first CoC book of standards, called the *Manual for Cancer Programs*, was published in 1996. It consisted of 6 standards and included an abstract form, a sheet to record follow-up information, and a rudimentary form that we now call a *site table* that included the age of patients and stages using Surveillance, Epidemiology, and End Results Program (SEER) summary stage. Other forms included a listing of survival data, which we had to manually compile using the life-table method, except that it also included survival

by stage according to the therapy received. There were also references for "Registry Uses and Reporting."

The first manual I worked with was called the *Cancer Program Manual*, followed by what we lovingly called the *DAM manual* (Data Acquisition Manual) in 1986. These manuals outlined how we were to do our work, what was a reportable case, how to code surgical procedures, and other essential information to inform us how to run a CoC-accredited registry. As we know, this evolved into Registry Operations and Data Standards (ROADS), then Facility Oncology Registry Data Standards (FORDS), and soon Standards for Oncology Registry Entry (STORE).

The National Cancer Database was started in 1989, and any hospital could voluntarily submit data. In 1996, all CoC-accredited hospitals were required to submit data, and in 2001, only CoC-accredited hospitals were allowed to submit and use data.

The National Cancer Registrars Association (NCRA), then called the National Tumor Registrars Association, was strictly a volunteer organization. Serving as a volunteer, at least from my point of view, was hit or miss. I remember asking to serve on a committee, sometimes never to be answered. In one case, I was told that I was on a committee, but never heard from the chair.

Tesla

1983 was a banner year for cancer registration. As we know, that was the year of the first certification examination. Our local and state registrars associations spent every meeting preparing us for it. The exam I sat for took place in a large auditorium at the University of Southern California. Of course, it was not computerized. Interestingly, the first 9 questions were so easy for me that I thought they must be trick questions. I now know that there are no trick questions on the certified tumor registrar (CTR) exam. There was many of us taking that first exam, and I believe that most of us passed.

That same year in Orange County, California (where I live), an epidemiologist at the University of California Irvine started a central registry involving 4 neighboring counties. This required us to submit our cases monthly. I believe we submitted the cases by floppy disk, something that no longer exists. In 1987, cancer became a reportable disease in the entire state of California. There were multiple regional registries that reported to the state central registry. Many of the regional registries have consolidated, so there are now fewer regional registries in the state.

1983 was also the first year that most registries in the state of California became computerized, although there were at least a few who had developed and were using their own facility-designed registry software before that. The state software was called CansurNet and was developed in collaboration with the CoC. This was followed the next year by Cnet (DOS version). This was provided to California hospitals free of charge, subsidized by the state of California. Unfortunately, California, like many states, can no longer afford to do that, so today California registries pay for Cnext (the Windows version). This also opened the door for many other software companies to successfully do business in the state.

TNM is now the required staging system. In 1991, all sites were to be staged using TNM, and physicians were required to stage beginning in 1995. Extent of Disease (EOD) staging was required for SEER registries beginning in 1988, replaced by Collaborative Stage (CS) in 1994. CS was required for all registries, not just SEER registries. Multiple Primary and Histology Rules (MPH) started in 2007, and the hematopoietic database started in 2010.

NCRA became a professionally run association. It still relies on volunteers, but through the work of the professional management team, has done much to elevate the cancer registry profession. We now are recognized as equal partners on the cancer team. Registrars sit on the committees of all the standard-setter organizations, and have a voice in how our profession is run. The NCRA Council on Certification initiated the guidelines for formal education for registrars, requiring a minimum of an AA degree.

In 1989, I realized that every hospital in California would need a registrar to report its cancer cases, even if it did not have a cancer program. I took a leap, left the hospital, and became a registry service provider as a contractor. I have since done state reporting, run hospital cancer registries for CoC-accredited hospitals, helped hospitals on a short-term basis when they were behind in abstracting, briefly acted as a clinical trials data manager, and once even helped a physician get ready to serve as an expert witness. There have been ups and downs, like not getting paid on occasion, but overall it has been very rewarding. The most rewarding part is getting to meet, work with, and make friends with colleagues all over the country.

Spaceship

We know that many changes have occurred through the years. In 2018 alone, there have been 9 updates, including the 8th edition of TNM, a new summary stage manual, ICD-O-3 changes, and the return of EOD. What does the future hold? Complete medical records on a computer chip? More registrars working remotely? Abstracting using a smartphone or another device not even invented yet? It will be interesting to see how medicine and cancer registration evolves. Perhaps some of us will be working on a spaceship. Starship Enterprise, anyone?

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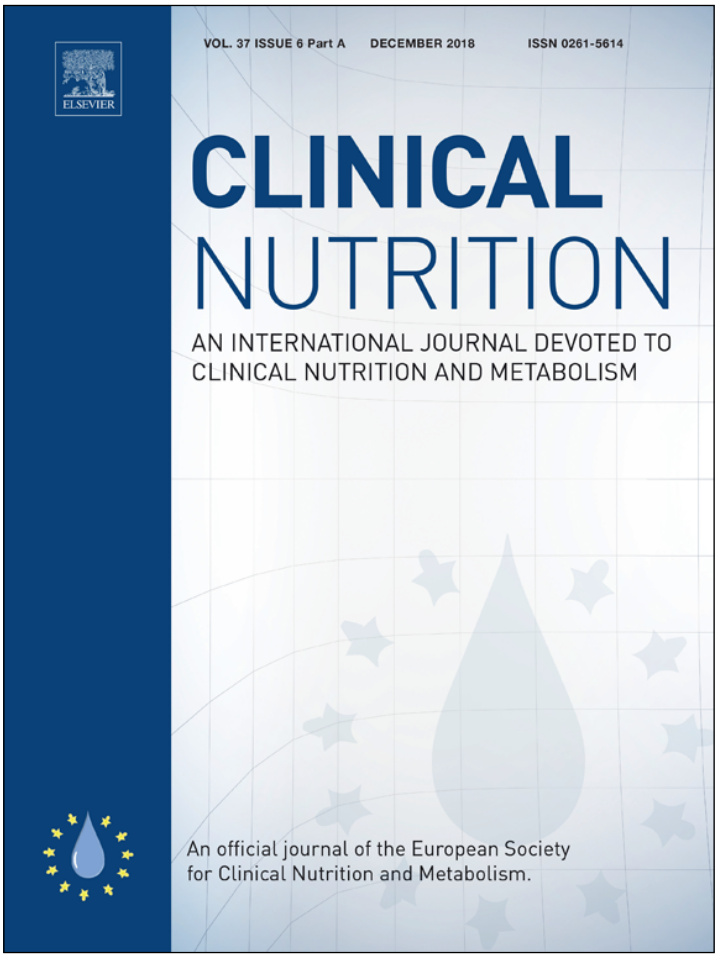

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Meta-analyses

Folic acid intake and folate status and colorectal cancer risk: A systematic review and meta-analysis

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SUMMARY

Background & aims: To evaluate the controversies among the studies assessing the association between folic acid intake or folate status and colorectal cancer risk.
Methods: PubMed, Cochrane library and references of related articles were searched from January 2000 to September 2016. Studies on folic acid intake or folate status and colorectal cancer or adenoma risk were included. Full text review was conducted for potentially eligible studies. Quality assessment was performed. Random-effects meta-analysis was used to estimate risk ratio and 95% Confidence Intervals. Analysis was conducted by Comprehensive Meta-Analysis software.
Results: Folic acid supplement intake showed no significant effect on colorectal cancer risk in meta-analysis of randomized controlled trials, RR: 1.07 (95% CI: 0.86–1.43). The effect on risk was not significant in cohort studies either; RR = 0.96 (95% CI: 0.76–1.21). However, there was significant reduced colorectal cancer risk in total folate intake in cohort studies; 0.71 (95% CI: 0.59–0.86). Odds Ratio was also significantly reduced in case control studies; 0.77 (95% CI: 0.62–0.95). Nevertheless once folate status was measured as Red Blood Cell folate content, no significant effect on colorectal cancer risk was observed; 1.05 (95% CI: 0.85–1.30).
Conclusion: The differences in bioavailability and metabolism of synthetic folic acid and natural dietary folate as well as variation in the baseline characteristics of subjects and various methods of folate status assessment might be the main reasons for these controversies. Findings of present study highlight the importance of individualized folic acid supplement intake given the fact that the beneficiary effects of long term folic acid supplementation is not confirmed.

1. Introduction

Folic Acid (FA), known as folacin, pteroylglutamic acid or vitamin B9, is abundant in green leafy vegetables, legumes and grains in form of folate [1]. The preventive effect of FA supplementation on birth defects led to fortification with FA in over 50 countries [2]. This mandate has resulted in a lower incidence of neural tube defects and meanwhile an increase in serum folate concentration [3].

Considering the possible dual role of FA in CRC, i.e. protecting normal cells meanwhile promoting precancerous cell growth,

Abbreviations: FA, folic acid; CRC, colorectal cancer; RCTs, randomized controlled trials; RR, relative risk; OR, odds ratio; RBC, red blood cell.

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numerous investigations have yielded controversial results on the beneficial effect of FA on the incidence of CRC. Some studies, including Randomized Controlled Trial (RCT) and cohort studies show beneficial effects of supplementary FA or dietary folate on the primary prevention of colorectal adenomas [4–8]. While a large RCT of seven years supplementation with FA, reported the need for further investigation to access the association of FA with higher risks of advanced adenomas [9]. Findings from this study highlighted the point that the transient increase in CRC incidence in the United States and Canada might be due to the implementation of FA fortification [10]. Supporting evidence by experimental studies shows that synthetic FA, with higher bioavailability compared to dietary folate, may lead to an elevated metabolized plasma FA [11], which is known as an inhibitor of natural killer cells cytokine inhibitors [12].

To date several meta-analysis have assessed the effect of FA supplementation on CRC risk. A recent meta-analysis of eight RCTs and another of combined analysis of three large RCTs did not find a significant effect on incidence of CRC [13,14]. However small sample sizes, differences in applied methodology and insufficient follow up time are among the shortcoming of included RCTs. Also two other meta-analysis of 10 RCTs and six RCTs found no beneficial effect of FA on various types of cancer risk and chemo-prevention of CRC [1,15]. Our analysis differs from the latter review studies in following aspects; 1) being a systematic review, 2) including more diverse population with longer follow-up time, 3) conducting stratified analysis based on FA supplement intake and blood levels/total/dietary folate.

Given the possible methodological insufficiency in so far performed meta-analysis, we hypothesized that a broader meta-analysis consisting of various related studies might be required to investigate the effect of FA supplementation and folate status on CRC risk. Therefore a systematic review and meta-analysis were conducted, not only including RCTs but also cohort and case control studies, to study firstly the impact of FA supplement intake and secondly that of folate status on CRC risk, in order to building a more consistent conclusion while addressing the root of discrepancies.

2. Materials and methods

2.1. Study protocol and search strategy

This study was performed according to PRISMA-P guidelines (Moher et al., 2009). PubMed and Cochrane library were systematically searched for studies published from January 2000 to September 2016, in English language, which have evaluated the relation between the intake of FA supplementation or folate status with the risk of CRC or adenoma (Fig. 1). MeSH terms for literature extraction from online resources were designed as following: ("Colorectal Neoplasms" or "colorectal neoplasm" or "colorectal cancer" or "colorectal Adenoma") and ("Folic Acid" or "Folic acid" or "Dietary folate" or "Total folate" or "red blood cell folate" or "Vitamin B9" or "Folate status"). The reference lists of the obtained articles were searched to identify any additional relevant articles on the same topic. The searching process was conducted under supervision of a medical librarian (KS).

A total of 1445 free full text citations were found. After title and abstract evaluation, 110 studies were retrieved for full text revision based on eligibility criteria. A total of 66 studies were excluded

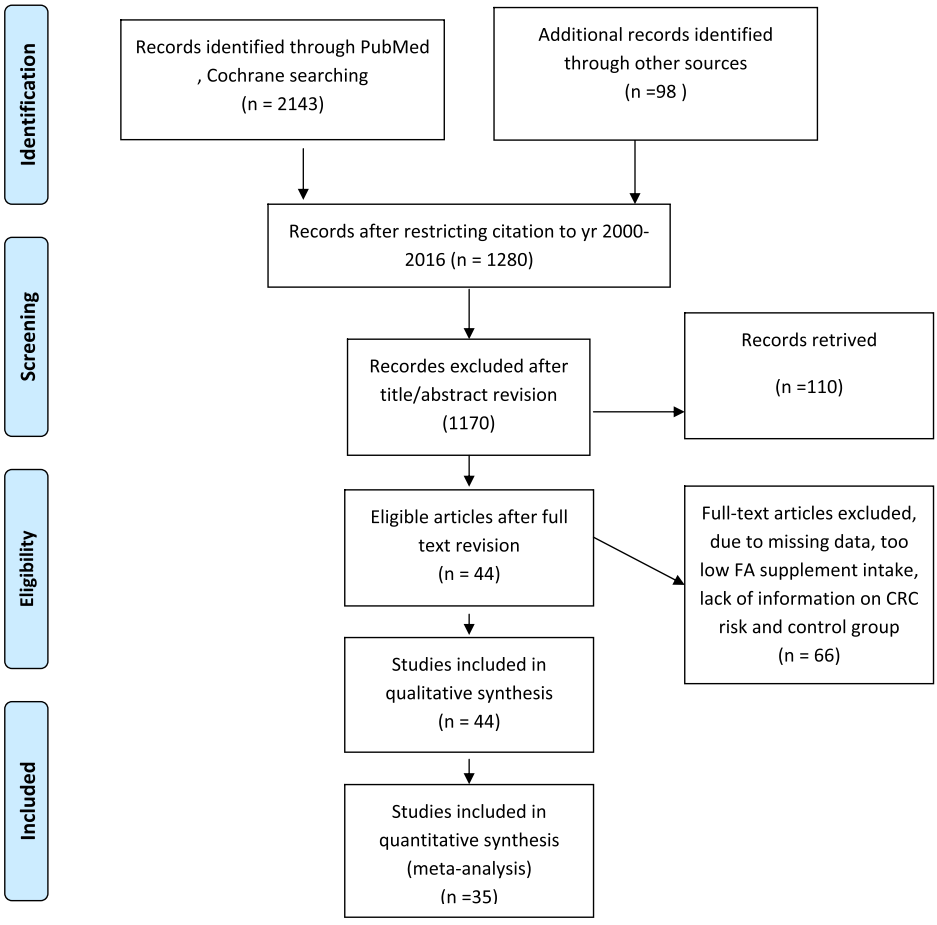

Fig. 1. Flow diagram of study selection process.

based on below mentioned eligibility criteria. Ultimately, 44 studies met the selection criteria (Fig. 1). Study data were extracted using standardized tables. All mentioned procedures were conducted by one investigator (SM). The entire procedure was monitored by a supervisor (SD).

2.2. RCTs

2.2.1. Eligibility criteria

Randomised controlled trails were included when supplementary FA level was specified. Studies were excluded when doses of FA supplement was lower than 0.5 mg/d (due to short period of trials lesser FA dose might fail to show the real effect), there were missing data on CRC or colorectal adenoma risk, lack of control group and incomplete data of desired covariates. Eventually 11 RCTs met the inclusion criteria.

2.2.2. Data extraction

Including the most adjusted RR for CRC, sample size, FA supplementation dosage and duration of intervention. Detailed study information on intervention and control groups is summarised in Table 1.

2.2.3. Quality assessment

Quality assessments for eligible RCTs were performed based on Jadad criteria including the following study specific characteristics

Table 1
Summary of eligible studies.

RCT studies

First author/year	Sample size		Dose of FA	Duration in month	CRC incidence		Score of quality
	FA	Placebo			Active	Control	
Cole 2007 [9]	516	505	1 mg	75	3	4	5
Logan 2008 [19]	432	421	0.5 mg	27	10	10	5
Wu 2009 [20]	338	334	1 mg	57	1	3	5
Gao 2013 [4]	430	430	1 mg	36	2	2	4
Lonn 2006 [21]	2758	2764	2.5 mg	60	50	37	5
Zhang 2008 [52]	2721	2721	2.5 mg	88	18	22	3
Figueiredo 2008 [51]	510	510	1 mg	36	42	56	3
Song 2012 [53]	741	729	2.5 mg	110.4	54	49	3
Armitage 2010 [18]	6033	6031	2 mg	80	86	91	5
Hankey 2012 [17]	4089	4075	2.5 mg	36	21	21	5
Jaszewski [57]	49	45	5 mg	36	39	32	3

Cohort studies

First author/year	Population		Adjusted for fibre	Outcome	Follow up yrs.	Adjusted for vitamins	Quality score
	Total	Cancer incidence					
Lee 2011 [7]	1,312,987	2299	No	CRC	16	Yes	8
Su 2001 [25]	10,183	219	No	CC	20	Yes	7
Martinez 2004 [23]	1014	219	-	Adenoma	5	–	5
Konings 2002 [6]	120,852	1171	Yes	CRC	7.3	Yes	7
Kabat 2008 [31]	89,835	617	No	CRC	16.4	Yes	8
Zschäbitz 2013 [29]	88,045	1003	No	CRC	11	Yes	8
Oaks 2010 [24]	109,175	219	No	CRC	6.5	Yes	9
Gibson 2011 [5]	525,488	7212	Yes	CRC	9.1	Yes	8
Zhang 2006 [26]	37,916	220	No	CRC	10.1	Yes	7
Bassett 2013 [30]	41,514	910	yes	CRC	15	Yes	8
Schernhammer 2010 [27]	173,230	609	No	CRC	22	Yes	9
Stevens 2011 [28]	99,523	1023	-	CRA	8	–	7
Terry 2002 [32]	56,837	389	Yes	CRC	10	Yes	8
de Vogel 2008 [33]	120,852	2676	Yes	CRC	13	Yes	8

Case control studies

First author/year	Population		Adjusted for fibre	Cancer	Adjusted for vitamins	Quality score
	Case	Control				
Van Guelpen 2006 [34]	226	437	No	CRC	No	8
Kato 1999 [35]	105	523	No	CRC	No	7
Glynn 1996 [42]	144	276	Yes	CRC	Yes	8
Takata 2014 [36]	288	575	No	CRC	Yes	8
Lee 2012 [22]	602	1130	No	CRC	Yes	8
Otani 2008 [58]	375	750	Yes	CRC	Yes	8
Gylling 2014 [37]	331	662	No	CRC	No	8
Weinstein 2008 [38]	277	278	No	CRC	Yes	8
Shrubsole 2009 [39]	303	1188	Yes	CRC	Yes	6
Bird 1995 [8]	332	350	yes	Adenoma	–	8
Kim 2012 [41]	787	656	No	CRC	Yes	7
Neuhouser 2015 [40]	988	988	No	CRC	No	8
Connelly-Frost 2009 [43]	643	1048	yes	CRC	Yes	7
Huang 2012 [48]	370	493	No	CRC	Yes	7
Carlo LA/2002 [44]	1953	4154	Yes	CRC	Yes	8
Lightfoot 2008 [49]	500	742	No	CRC	Yes	5
Liu 2013 [45]	1609	1974	yes	CRC	Yes	7
Murtaugh 2007 [46]	751	979	Yes	CRC	Yes	7
van den Donk 2005 [47]	751	701	Yes	CRC	Yes	7

of randomization, random numbers generation, reporting of dropouts and withdrawals and blinded allocation [16]. When any of these characteristics was presented, a point was given, yielding a range score of Zero to Five. Six articles were of the highest quality based on quality assessment [9,17–21].

2.3. Cohort studies

2.3.1. Eligibility criteria

Included of studies to have over 50 incident colorectal cancer cases; precise method for assessing dietary folate status but not need to be the same as others; identification of incident CRC by using follow up questionnaire [22–28] or subsequent medical record review [29,30], linkage with a cancer registry [5,6,30–33] or linkage with a death registry [7,25–27,31,32]. After full text evaluation, 14 cohort studies were included.

2.3.2. Data extraction

Including the most adjusted RR for CRC for dietary/total folate intake, total population, adjustments for fibre, outcome, adjustments for vitamins, duration of follow up and quality score (Table 1).

2.3.3. Quality assessment

Eligible studies were scored based on Newcastle–Ottawa scale. Each feature in scale was given one point yielding score of zero to nine. Five studies were of the highest quality [5,6,22,24,32]. All 14 studies were given the complete score in terms of matched control group by sex and age and controlling at least three more covariates in the statistical analysis. Four cohort studies got the highest score in exposure section considering independent blind outcome assessment, adequate follow up period (>10 yrs) [24,29,31,32].

2.4. Case control studies

2.4.1. Eligibility criteria

Nested case control or studies with at least 300 cases; information on FA status had to be circulating (plasma, serum or RBC) levels FA [8,22,34–42] or total/dietary folate intake [36,41–49] and the outcome had to be CRC [22,34–42] or colorectal adenoma [8]. Nineteen studies were included.

2.4.2. Data extraction

The most adjusted OR for CRC, number of cases and controls, adjustments for fibre and vitamins and quality score were extracted (Table 1).

2.4.3. Quality assessment

Studies were scored using Newcastle-Ottawa scale based on eight characteristics. Fourteen studies were scored seven out of eight. One study lacked information on adequate case definition [46] and four studies lost one point due to selecting non community based controls [39,41,44,49]. The detailed characteristics of eligible studies are provided in Supplementary Table 1.

2.5. Data analyses

2.5.1. Pooling based on folic acid supplement intake

The risk for FA supplement intake and CRC or adenoma was extracted from RCTs and cohort studies (Fig. 2).

For pooling overall, the RR for CRC or adenoma was extracted from eligible RCTs and the most adjusted RR for CRC was extracted from cohort studies. An overall RR was computed separately for CRC and adenoma in RCTs and for CRC in cohort studies.

2.5.2. Pooling based on folate status

The most adjusted risk for highest levels of dietary or total folate intake for CRC was extracted from eligible cohort studies and the most adjusted risk for total folate or RBC or plasma folate was extracted from case control studies (Fig. 3).

Predictive interval of mean effect of Supplementation with FA and folate status was calculated using incorporated modules of meta-analysis tools (see https://www.meta-analysis.com/pages/prediction.php).

An overall risk was computed separately for each subgroup of folate status in cohort and case control studies.

Cochran's Q statistic-value, I^2 Index were used to test homogeneity assumption across the studies. Random-effects models were used to compute the overall RR of CRC for each group of studies due to significant heterogeneity among studies [50]. Publication Bias among studies was assessed using Egger test (Figs. 4 and 5). Analyses were conducted by Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey).

3. Results

3.1. Folic acid supplement intake and CRC risk

Thirteen studies were included in final analysis, consisting of 35,761 subjects in RCTs and 1,926,520 in cohort studies. There was a significant publication bias in FA supplement subgroup, Egger bias: 1.67 (95% CI: 0.05–2.66, $P = 0.01$). No significant heterogeneity was observed in eligible cohort studies, $I^2 = 0.00$ (Q: 0.25, $P_{het} = 0.88$). There was a significant heterogeneity among RCTs, $I^2 = 68.92$ (Q: 25.84, $P_{het} = 0.001$). Studies with most extreme findings from the overall finding were detected [9,51,52] using forest plot (Fig. 2). Sensitivity analysis was done; there was no significant change in overall results. However the publication bias became nun-significant after running sensitivity analysis for the study causing asymmetry in funnel plot [4].

Overall, we observed supplementary FA had no significant adverse effect on the risk of CRC in RCTs with a pooled risk of RR: 1.07 (95% CI: 0.86–1.43). The effect remains non significant once the mean effect and the Prediction Interval (PI) was estimated; 1.00 (95% PI: 0.69–1.45). Cohort studies showed a pooled risk of 0.96 (95% CI: 0.76–1.21), with the mean effect of 0.96 (95% PI: 0.23–3.86). There also was no significant effect on adenoma risk in RCTs; 1.00 (95% CI: 0.86–1.51).

3.2. Folate status and CRC risk

Twenty two studies were included in final analysis, consisting of 2,520,112 subjects in cohort and 12,042 in case control studies. No significant bias was detected in folate status subgroup, Egger bias: 1.60 (95% CI: 0.57–1.77, $P = 0.30$). There was a significant heterogeneity among cohort studies, $I^2 = 51.16$ (Q: 31.07, $P_{het} = 0.00$). Also in case control studies a significant heterogeneity was detected, $I^2 = 58.90$ (Q: 48.65, $P_{het} = 0.00$). Random effect was used for calculating overall risks in both cohort and case control studies.

Two studies [8,42] with most extreme findings from overall risks were detected using forest and funnel plots (Figs. 4 and 5). There were no significant changes in overall results after running sensitivity analysis, though the symmetry in funnel plot was enhanced.

The risk of CRC and total folate intake showed a significant inverse association among eligible cohort studies; 0.71 (95% CI: 0.59–0.86). The mean effect was 0.96 (%95 PI: 0.23–3.86). Also in case control studies there was a significant inverse association; 0.77 (95% CI: 0.62–0.95, Fig. 3), the mean effect was 0.75 (%95 PI:

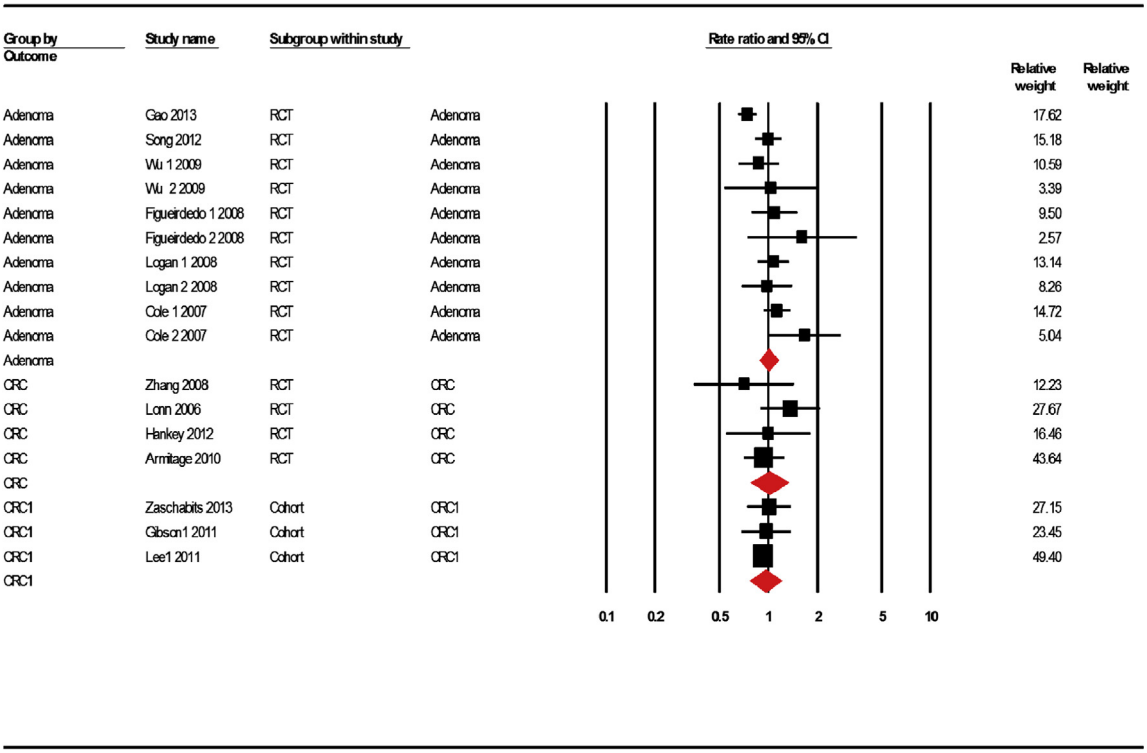

Fig. 2. Forest plot of RTCs and cohort studies reporting the RR for FA supplement intake treatment with respect to CRC or advanced adenoma. Weights are from random effects analysis. The square dots present the risk reported by each study. The diamond presents overall risk for each subgroup.

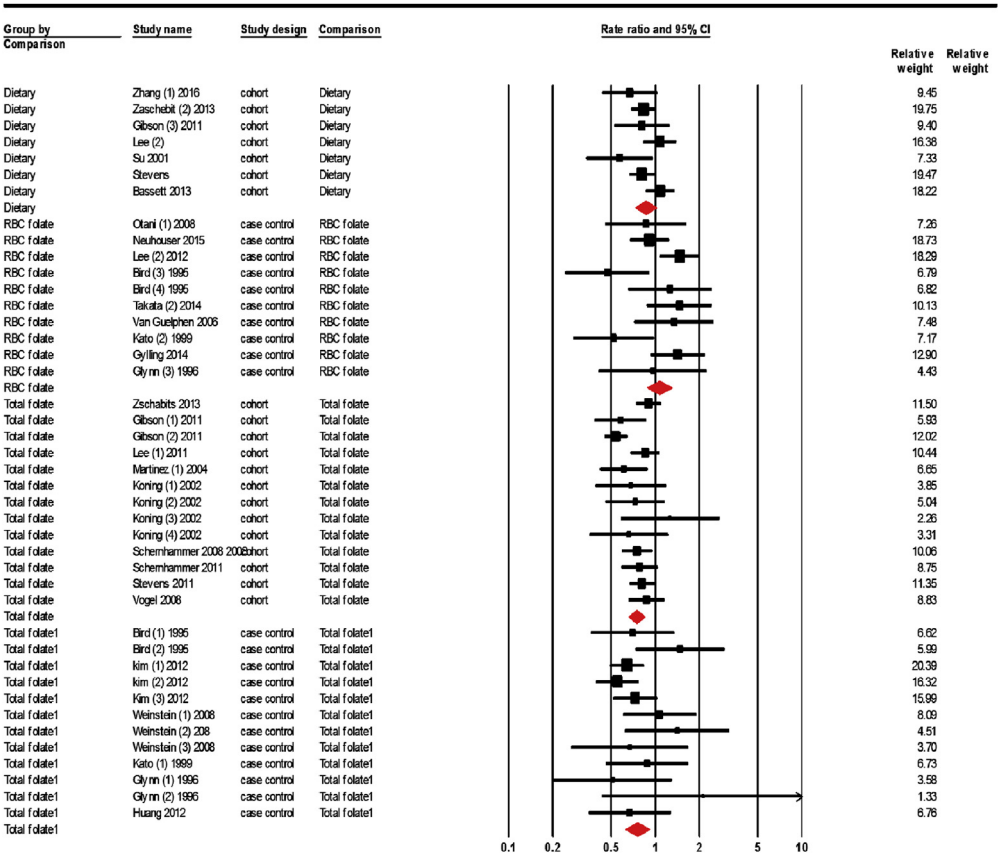

Fig. 3. Forest plot of cohort and case control studies reporting the RR for folate status (Dietary folate/total folate/RBC folate) with respect to CRC. Weights are from random effects analysis. The square dots present the risk reported by each study. The diamond presents overall risk for each subgroup.

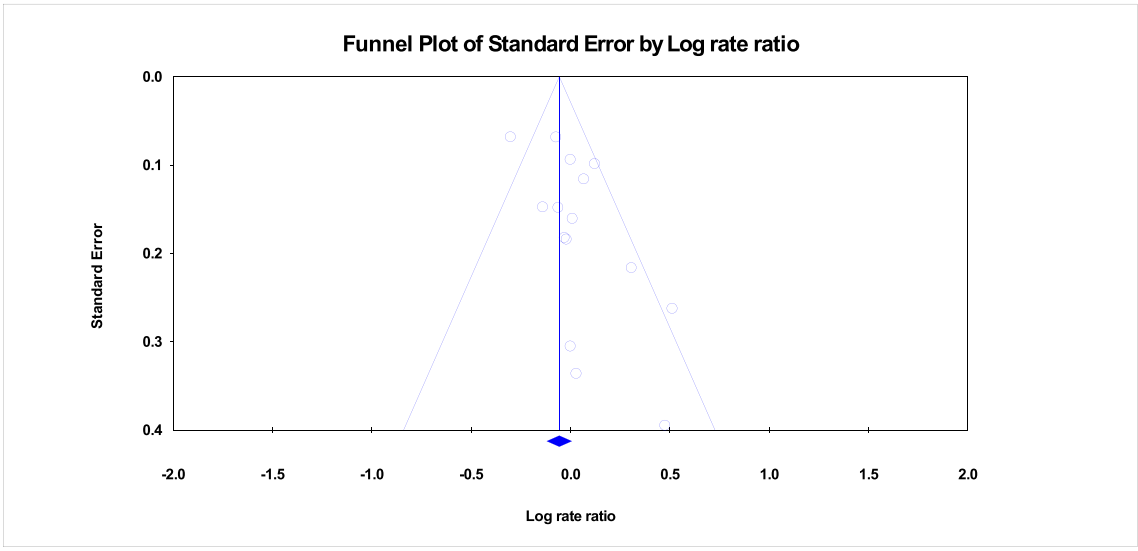

Fig. 4. Begg's funnel plot for eligible RCTs and cohort studies assessing FA supplementation and CRC risk. Bias indicators; Begg-Mazumdar: Kendall's tau = 0.31, $P = 0.10$, Egger: bias = 1.67 (95% CI = 0.26–3.09).

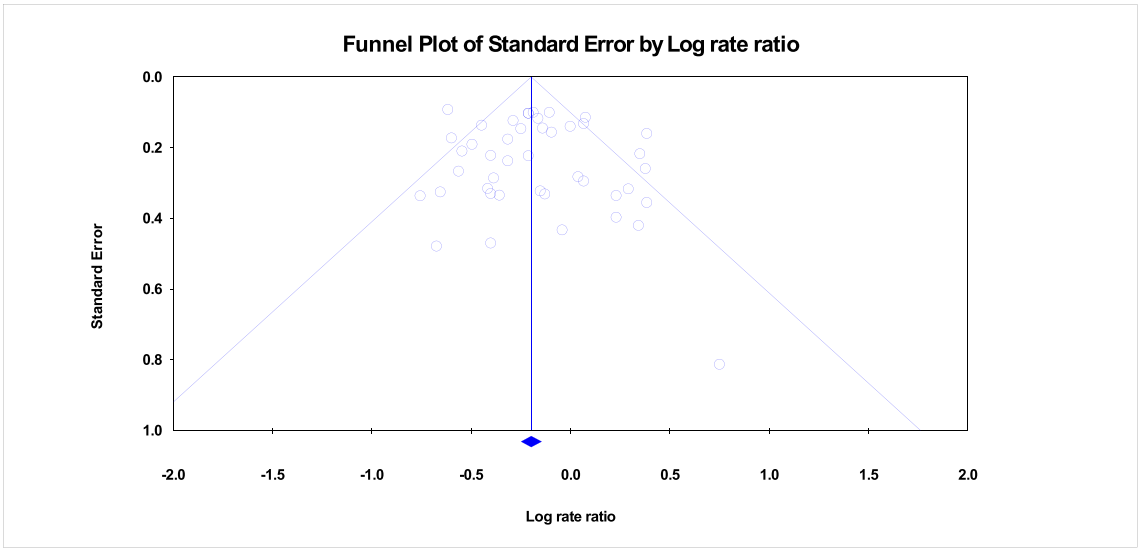

Fig. 5. Begg's funnel plot for eligible cohort and case control studies assessing folate status and CRC risk. Bias indicators; Begg-Mazumdar: Kendall's tau = 0.44, $P = 0.67$, Egger: bias = 0.42 (95% CI = −0.56 to 1.40).

0.52–1.04). There was no significant association between overall risk and RBC and plasma folate levels; 1.05 (95% CI: 0.85–1.30).

4. Discussion

We assessed the role of FA supplement intake and folate status in the risk of CRC or adenoma in a meta-analysis of RCTs, cohort and case control studies. The bioavailability and metabolism of synthetic FA and natural dietary folate are different [11], therefore a broader meta-analysis was conducted with separate FA and folate subgroups in analysis. To best of our knowledge, it is for the first time that a systematic review and meta analysis including all types of controlled studies was conducted with the aim of pointing the root of discrepancies. Total folate intake was associated with a reduced risk of CRC in cohort and case control studies, while there was no significant association between CRC or adenoma risk and supplementary FA subgroup neither in RCTs and cohort studies nor in RBC folate in case control studies.

4.1. Folic acid supplement intake

No significant effect was observed on overall risk of CRC or adenoma in the preliminary analysis of four RCTs reporting the risk for CRC [17,18,21,52] and six RCTs [4,9,19,20,51,53] reporting the risk for adenoma. Among the eligible RCTs, only Gao et al. reported a significant reduction in risk of advanced adenoma after supplementation with FA for three years. The subjects of this study were confirmed to be free from any adenoma by colonoscopy before the intervention and they have also a lower baseline folate levels, taking the mentioned factors in to account the beneficial effects of FA supplement intake may not be generalizable. Our overall findings were in agreement with the recent meta-analyses by Qin et al.

and Carroll et al. [14,15] where no effect of FA supplementation were found on the risk of CRC by combining eight and six preceding RCTs. Likewise Figueiredo et al. found no effect of FA supplement on CRA in a combined analysis of three RCT with mean 3.5 years of follow up [13]. An example of controversies with the findings of Gao et al. study [4] is a report of 67% increase in risk of advanced adenoma by FA supplementation by Cole et al. [9] during only 35 months period of intervention and with a lesser dose of FA (1 mg/d). However in the study of Cole et al. [9] the history of adenoma in subjects and randomizing the intervention group to receive aspirin might have influenced the exact effect of FA supplementation on adenoma re-occurrence. Therefore, in such reports like Cole et al., a careful assessment of modifying controlled factors is essential. Another example is intervention group by Song et al. [53] who took vitamin B6 and B12 along with FA supplementation. There is a possible chance that the undesirable effect of FA supplementation might have been attenuated by vitamins intake. The mean duration of follow up in eligible RCTs in this meta-analysis is 5.4 years, while CRC sequence would possibly take as long time as 10 years [5]. While a short follow-up period of RCT may raise some concerns about the observed associations, Song et al. [53], in intervention of 110 months reported a similar result. While the collective evidence support for no association, few individual studies report interesting findings. Therefore, the observed non-significant effect on overall risk of CRC or advanced adenoma by FA supplementation seems to be underestimated due to underpowered studies and short follow-up period. Furthermore the overall risk in three cohort studies [5,7,29] reporting FA supplement intake also remained non-significant. The precision of used method for assessing FA intake in cohort studies could be approved since the latter results are in agreement with that of eligible RCTs. In summary, there was no significant association in the risk of CRC or adenoma in supplementary FA subgroup neither in RCTs nor in cohort studies and in their combined analyses.

4.2. Folate status

There was a significant lower risk of CRC in total folate intake in both subgroups of cohort and case control studies. Our findings are in line with the findings of Kim et al. pooled-analysis [54], likely due to similarities in applied methods eligible studies. However, another meta-analysis showed a null effect of total folate on CRC [55], which used data from only three studies being only one study, reported risk for both genders. In present meta-analysis a more reliable conclusion is offered due to using data from a larger pool of 10 cohorts and 12 case control studies to estimate overall risk.

Risk of CRC showed no significant reduction in category of dietary folate intake in cohort studies. This finding is in agreement with that of Kim et al. [54]. In prospective studies, it is not possible to elucidate the true effect of dietary folate on CRC. In driving such a conclusion, one may consider other healthy behaviours such as other dietary factors, lifestyle and increased level of precancerous lesions screenings which are naturally more improved in individuals with higher total folate intake. The influence of MTHFR C677T genotype on the effect of total folate on CRC might also be a factor in discrepancies, given the effect of total folate on CRC differs from 60% to 38% reduced risk in TT homozygote compared to CC/CT [41]. Considering the observed different effect of total and dietary folate on CRC risk, a precise unified method of folate status assessment in cohort and case control studies are needed.

Our study revealed no association of RBC folate level with CRC. Other found a similar result [55]. Given eight eligible case control studies were nested within large cohort studies (except for one study [8]) the reliability of results is likely to be near to cohort studies. None significant association of RBC folate status with CRC risk in the present analyses may reveal a possible effect of confounding factors masking the possible true negative effects. However it is noteworthy that RBC folate might be affected by other B vitamin status specially B12 deficiencies [56]. We therefore performed a sub-analysis and found a significant increased risk of CRC in studies reporting plasma folate levels in both genders. Here the study by Lee et al. [22] found 47% increased risk of CRC highest quartile of plasma folate compared to the lowest quartile nested in three large cohort studies. Van Guelpen et al. also [34] reported a significant increased risk of CRC in highest quintile of plasma folate. One concern over these studies is the lack of data over the baseline plasma folate levels and also plasma folate is not an indicator of long-term intake of folate compared to RBC folate [56]. The results of latter studies highlight the possibility of adverse effect of higher folate intake on CRC risk. Findings from the present analysis offer the possibility of undesired effect of higher folate status on CRC risk.While methylation in some group of genes can benefit cells protection, methylation in specific genes promotors such as CpG Island is regarded as a trigger to tumorigenesis in normal mucosal colorectal cells. The mentioned mechanism might be an explanation to the possible adverse effect of FA supplementation in CRC.

4.3. The involved factors in discrepancies among studies

The discrepancies among the results of FA and folate status subgroups might be partially due to differences in bioavailability and metabolism of synthetic FA and natural folate. The positive association of higher total folate could also have been augmented by confounding factors, which are naturally accompanied by higher folate intake or regularly multivitamin use. Using RBC folate and/or un-metabolized plasma folate at baseline and after the incidence of CRC in prospective studies may solve this concern; given RBC folate is an objective index of folate status [56]. Other factors such as underlying mechanisms leading to higher risk of CRC in various studies population, genetic influences, differences in assessing folate status etc. might be responsible for discrepancies.

4.4. Study limitations

In the present study the data have been extracted by one investigator in a supervised fashion (SM, SD). Although a second reader on data extraction was not available, our supervised data extraction method yielded almost a comparable results and conclusion as previous studies. Moreover it was not possible to detect a subgroup of eligible studies to assess the impact of fortification period on risk of CRC. There also is no consensus over the definition of higher folate status. The other limitations are shorter follow up time, combination of FA with other vitamins and aspirin adjunct therapies in most of the eligible studies.

In conclusion no significant increase in CRC incident overall risk was observed in FA subgroup. Given the observed discrepancies between studies [4,9,53], in addition to highlighting the importance of individualized dose and duration of supplementation with FA, it is crucial to investigate the exact effect of FA supplementation/fortification on the incidence of CRC when taking to account possible confounding factor such as genetic factors of folate metabolism in future studies.

Contribution

SM designed the study, carried out the study, ran the data analyses and prepared the first draft of manuscript. SD designed the study, conceived the study and edited the manuscript. GB, BZA, commented on study design, data analyses, inference of results and critically editing the manuscript. RD, JST and JSH participated in the

study design, performed the statistical analyses and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interest

This study was financially supported by Research Vice Chancellor of Tabriz University of Medical Sciences (grant numbers: TBZMED.REC.1394.1193). The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.10.010.

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Research Article

Uses, Limitations, and Validity of a Registry of Congenital Anomalies in Iran: A Critical Review

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Background and Aims. Preventive strategies of congenital anomalies are basically relying on the systematic ongoing collection and analysis of data and timely dissemination of information. The aim of this paper is to briefly report a critical review of a surveillance system of congenital anomalies in a developing country, by describing the challenges and experience of the registry since it began. *Methods*. Tabriz Registry of Congenital Anomalies (TRoCA) was mainly set up based on the guidelines provided by the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) for data collection, coding, process, analysis, use, and evaluation of the system. *Findings*. TRoCA has successfully achieved its main objective as a pilot model for setting up a nationwide registry of congenital anomalies in the country. The programme has too succeeded in relation to its regional objectives: epidemiological rates and data have been produced consistently for etiological investigations, methodological studies, service provision, and preventive measures for selected anomalies. *Conclusions*. Our successful experience, as a small registry in a developing country, might be of interest and useful to practitioners, policymakers of birth defects control programmes, and mainly those willing to set up a monitoring system of congenital anomalies in similar areas.

1. Introduction

Birth defects are making a proportionally major contribution to perinatal mortality, childhood morbidity, and disability in many countries. Occurrence of congenital disorders varies between different countries ranging from 2 to 10 percent of births [1, 2].

The prevention of congenital anomalies requires prior knowledge of the aetiology and causal factors involved. Although aetiology is still largely unknown, preventive methods are now available for about 60 percent of congenital abnormalities [3, 4]. Preventive strategies, on the other hand, are basically relying on the surveillance, systematic ongoing collection and analysis of data, and timely dissemination of information. To assure the quality of these measures, critical review of the procedures for evaluation purposes has previously been introduced for monitoring systems [5, 6].

The aim of this paper is to briefly report a critical review of a monitoring system of congenital anomalies in Iran, by describing the challenges and experience of the registry since it began.

2. Methods

2.1. Tabriz Registry of Congenital Anomalies. In 2000, a project was carried out in the Tabriz city of Iran to investigate the epidemiology of congenital anomalies. The aim of the study was to provide baseline information to set up a regional registry of birth defects for the first time in the country. This programme was then called Tabriz Registry of Congenital Anomalies (TRoCA) [7]. Our programme was also accepted in the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), and European

network of registries for congenital anomalies (EUROCAT) as a member of countries having an established registry for birth defects [1, 2].

Some of the registry systems of the ICBDSR and EUROCAT members were studied in terms of data collection, process, analysis, use, and evaluation of the system to determine the requirements for setting up a local registry in Iran. The minimum requirements for the registry were also determined.

TRoCA is located in Tabriz city run under the Tabriz University of Medical Sciences. Tabriz is one of the three major cities in Iran, located in the northwest region. Tabriz University of Medical Sciences is one of the five top universities in the country providing medical and health services for the population in the northwest of Iran. TRoCA has been financially supported by local and national funds.

2.2. Objectives. The principal aims of TRoCA programme are to establish a monitoring system of congenital anomalies in the region and to implement control and preventive tasks in the area. It was primarily intended to use TRoCA framework as a pilot model for setting up a surveillance of birth defects in the whole country. Purposes of TRoCA are to

(i) register the occurrence of selected birth defects in the region,

(ii) prepare epidemiological indexes to indicate the magnitude and trends over time,

(iii) monitor emerging or unusually high occurrences of congenital anomalies,

(iv) make valid data available to policymakers,

(v) plan and implement preventive and control strategies to prevent selected anomalies,

(vi) evaluate prevention and control strategies.

2.3. The Registration Process and Methodology. Prenatal care is routinely provided for every pregnant woman on a regular basis (up to eight times) with 1–3 diagnostic sonographies during pregnancy. If needed, further diagnostic procedures (i.e., genetic tests for congenital anomalies, etc.) are performed. Termination of pregnancies is permitted for a few selected anomalies. TRoCA reports termination rate for major malformations only. After birth, all children in three hospitals involved in the programme are normally examined by a gynaecologist, obstetrician, neonatologist, or pediatrician at birth. They are followed up until hospital discharge for general health status, maturity, and congenital anomalies. The TRoCA programme covers about 15,000 births (annual average) in the area with about 300–400 newborns with one of the anomalies in this population. Background information and basic characteristic data are gathered for all births in TRoCA region. Some additional information (i.e., family history, parity, parental age, residence, education, maternal illness, gestational length, birth weight, and type of birth) is also available for infants with anomaly and mothers. Karyotype and autopsy are not routinely performed unless it is requested as a necessity after full clinical investigation.

We use a "passive" method of data collection. The responsible persons (as registrar) for data documentation are midwives. A medical coder has been assigned in this programme to code/classify the defects. The end users defined the congenital anomalies for the purposes of this programme based on the standard coding system of the International Classification of Diseases (ICD) under one of the following main headings according to the primary diagnosis of anomaly:

(i) Nervous system anomalies;

(ii) Genitourinary tract and kidney;

(iii) Anomalies of limb;

(iv) Chromosomal anomalies;

(v) Cleft lip with/without palate;

(vi) Congenital heart disease;

(vii) Musculoskeletal and connective tissue anomalies;

(viii) Digestive system anomalies;

(ix) Eye and ear anomalies;

(x) Other anomalies.

Total prevalence is calculated by dividing the numerator (registered cases of congenital anomalies in the TRoCA region) by the relevant denominator (total live and stillbirths in the TRoCA region) for the same period of time. An infant/fetus with more than one anomaly is counted once only in the numerator. The main criteria of inclusion of fetal deaths or stillbirths in data analysis are pathologic confirmation of the defect provided by the hospitals. Time trend analysis, relative frequencies, and confidence intervals are also calculated for some statistical purposes. For more details of the methodology, TRoCA publications may be searched.

2.4. Ethics. TRoCA activities have been approved by the Ethics Committee of the Tabriz University of Medical Sciences. Confidentiality and privacy of identity-related information are strictly considered in every part of the data gathering, handling, processing, registration, access, and reports.

3. Findings

3.1. Uses of TRoCA in Relation to Its Objectives

3.1.1. Detection of Epidemics. To date, generally, our data shows no epidemic of any of kinds of birth defects in the area. However, an unusual increase occurred for the total prevalence of congenital anomalies in 2002 in the registry region. We then identified that this happened due to an improvement in case ascertainment.

3.1.2. Time Trends. As seen in Figure 1, there is a steady increase in the occurrence of congenital anomalies in the region over time. Total prevalence of anomalies is more than tripled ranging from 104.6 (per 10,000 births) in 2000 to 326.5 (per 10,000 births) in 2014. During this period of time, early

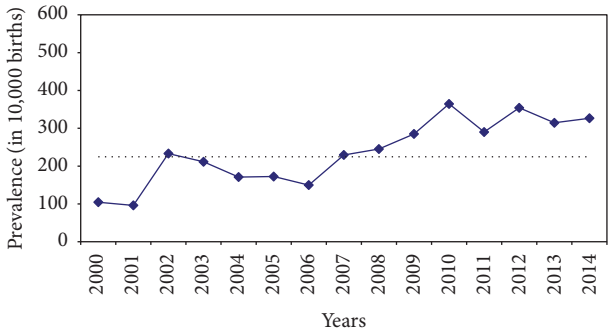

Figure 1: Time trend of prevalence of congenital anomalies (Tabriz, Iran) (dotted line shows the total prevalence in average).

records show that nervous system and genitourinary tract anomalies were the most frequent defects while later data indicated that heart and limb defects are the most common ones (Figure 2).

3.1.3. Estimates of Prevalence. A total of 261 024 births were registered in the region over the study period including 258 153 (98.9%) live births and 2871 (1.1%) stillbirths. During this period, 5870 cases with a primary diagnosis of congenital anomaly were ascertained, representing an overall prevalence rate of 224.9 per 10,000 births. Genitourinary tract and kidney anomalies, limb defects, anomalies of nervous system, and congenital heart diseases accounted proportionally for more than 65 percent of anomalies in the region (Figure 3).

3.1.4. Geographical Variations. Table 1 shows the prevalence (in 10,000 births) of selected congenital anomalies in 13 ICBDSR registries across the globe published in 2014 for the data between 2007 and 2011 [2]. The rate of total limb reduction defects in TRoCA is almost nine times, in average, higher than that of other regions. Tabriz displays almost similar rates for other groups of birth defects compared to other registries, although the rate of anencephaly, hydrocephaly, and cleft palate is still high in the region while spina bifida shows a low rate.

3.1.5. Special Studies. Data provided by TRoCA have resulted in a study to estimate the missing frequency of congenital cardiac anomalies at the time of delivery and birth in the region. Accordingly, 59.1% of children with congenital heart diseases were not identified at birth [8].

We found that the accuracy of family physicians in case detection and diagnosis of congenital anomalies in rural areas is more than 98% [9]. We also investigated the occurrence rate (33 percent) of termination in pregnancies with congenital anomalies [10], and association of folic acid consumption and birth defects [11]. More other studies have been carried out using our registry data. For details, TRoCA publications need to be searched.

3.1.6. Response to the Needs and Services. In addition to the registration of birth defects, TRoCA has extended its activities to implement control and preventive services for genetic disorders and congenital anomalies in the region. This includes genetic services to families who have a history of an anomaly/disorder in the family, and preconceptional programmes for young couples. This new programme called Tabriz Foundation for Public Health Genetics (TFPHG) was launched in 2013 [12].

3.1.7. Etiological Studies. General information is routinely collected for every neonate. Some exposure information is also available of mothers of all malformed infants. Other women giving births in the TRoCA maternity and children hospitals with normal newborns routinely complete the similar data form. They might be considered as matched control group. Using these data of control group plus routine statistics from general population [13], testing of etiological hypotheses and investigation of the role of some exposures are virtually possible in TRoCA registry.

3.2. Limitations of TRoCA

3.2.1. Epidemiological Pitfalls. TRoCA is always able to describe the distribution and occurrence of congenital anomalies in its defined population (by time, place, and other influencing factors). However, epidemiological reliability and representativeness of the rates captured by the programme have not been fully investigated yet. The timeliness of the information provided by TRoCA is also still a matter of epidemiological pitfall where the programme is able to release primary information on the occurrence of congenital anomalies at least one year after the data collection.

As indicated before, TRoCA programme monitors about 15,000 births (annual average) in the area with about 300–400 cases with one of the defects in the newborns. The very small frequency and the rare nature of some groups of anomalies influence the epidemiological power of the rates and occurrence patterns of various types of congenital anomalies provided by the programme.

3.2.2. Delayed Ascertainment. Multiple sources of case ascertainment result in a true pattern of birth defects in the population. The data of TRoCA comes mainly from two maternity hospitals plus a referral medical centre for sick children in the region. Some anomalies are routinely not diagnosed until some times after birth. For this reason, ascertainment of those defects is inevitably delayed. Nearly 60% of children born with congenital heart disease, for example, were not ascertained by TRoCA at birth. They were then identified as having heart defects in children hospital during the next 12 months after birth [8]. The delayed ascertainment, therefore, appears to be an inevitable part of the registry.

3.2.3. Variable Validity of Data over Time. At birth, nervous system anomalies were ranked first in the TRoCA earlier years' data while the first rank belongs to congenital heart defects in recent years' records (Figure 2). The reason is that the improvement of the diagnosis and identification of congenital heart defects over time have resulted in a complete ascertainment of these groups of anomalies in the registry.

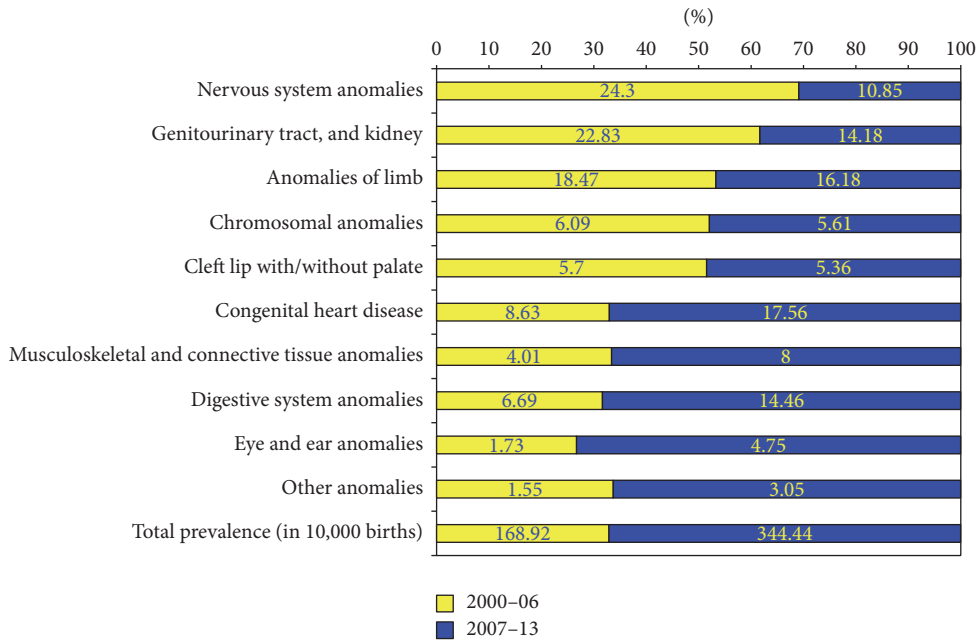

Figure 2: Comparison of the defects proportion (%) between 2000–06 and 2007–13 (the last bar shows the total prevalence in 10,000 births).

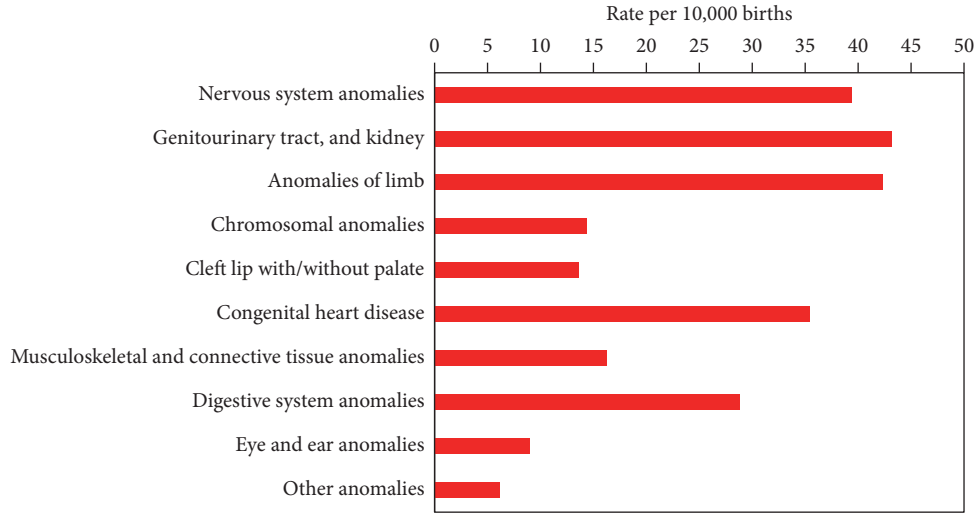

Figure 3: Prevalence of congenital anomalies (Tabriz, Iran).

This variation in the ascertainment over time appears to be an inevitable limitation of every registry including TRoCA.

4. Discussion

4.1. Has the TRoCA Succeeded? Tabriz Registry of Congenital Anomalies started its main activities in 2000. A nationwide registry of congenital anomalies in Iran was then established in 2012 based on the data, framework, and baseline structure provided by TRoCA (as a pilot programme). It is therefore believed that TRoCA has successfully achieved its main objective as a pilot model for the whole country.

TRoCA has too seemingly succeeded in relation to its regional objectives: annual prevalence rates have been produced consistently over years [7], geographical comparisons have been made possible by linking the TRoCA with international programmes [1, 2], and TRoCA has provided data for some specific investigations [10, 11], service provision for selected anomalies [8], and created a validated tool for family practitioners for case detection and diagnosis of birth defects [9]. In response to the health care needs of high risk population, TRoCA is implementing control and preventive services for some genetic disorders and anomalies in the region [12].

4.2. Main Challenges. TRoCA recorded a low rate for spina bifida, high rates for anencephaly, hydrocephaly, and cleft palate without cleft lip, and a very high rate of limb reduction defects in the region. While TRoCA examines and reports the annual rates of congenital anomalies consistently, we do

Table 1: Prevalence (in 10,000 births) of selected congenital anomalies in 13 ICBDSR registries[1, 6, 7].

Selected congenital anomalies	Australia: WARDA[2]	Canada	France: Paris	Germany: Saxony-Anhalt	India[3]	Iran: Tabriz	Italy: Tuscany	Japan	Malta[3]	Saudi Arabia[3]	South America[4]	Ukraine	USA: Texas
Anencephaly	5.5	1.2	4.9	2.0	11.8	**10.7**	1.5	0.7	1.5	10.1	5.8	7.0	2.7
Spina bifida	5.7	3.2	5.2	5.2	11.8	**1.4**	3.9	5.6	8.4	2.0	8.5	10.4	3.9
Cleft palate without cleft lip	10.2	6.4	6.4	5.9	1.7	**8.4**	3.3	5.1	14.3	2.0	4.5	7.2	5.9
Encephalocele	2.1	0.7	2.2	1.4	2.5	**1.0**	1.0	0.5	1.9	2.0	3.3	1.8	1.0
Microcephaly	3.8	3.7	2.4	11.7	1.4	**4.5**	0.6	1.6	4.5	12.1	4.8	5.9	12.9
Hydrocephaly	7.7	4.7	14.4	4.6	8.9	**13.8**	3.4	7.8	1.9	12.1	17.2	5.3	7.2
Cleft lip with or without cleft palate	10.8	9.4	8.2	12.1	4.6	**11.9**	5.2	21.7	10.9	14.1	11.7	7.8	10.4
Undescended testis	39.5	34.4	NR[5]	4.7	0.9	**9.8**	6.6	NR	NR	NR	9.8	31.6	13.7
Hypospadias	34.6	27.5	17.3	6.9	1.8	**19.8**	13.9	5.2	22.7	14.1	9.2	2.8	16.6
Limb reduction defects	7.0	3.3	6.1	7.7	4.2	**51.0**	4.2	3.8	7.4	4.0	7.6	4.8	6.0
Polydactyly	12.1	13.2	1.9	5.5	3.2	**8.0**	1.1	6.7	17.3	10.1	3.1	4.1	4.0
Tetralogy of fallot	2.9	3.4	4.1	2.8	0.4	**1.4**	2.3	7.0	2.9	6.0	1.6	2.7	3.9
Coarctation of aorta	4.3	4.5	3.8	5.4	0.1	**2.9**	2.3	6.7	3.5	2.0	0.5	1.7	5.2
Hypoplastic left heart syndrome	2.2	2.4	3.1	2.7	1.1	**3.7**	2.6	4.5	5.9	4.0	0.9	2.0	2.2

Notes. [1] Data based on the annual report (2014) published by the International Clearinghouse for Birth Defects, Surveillance and Research (ICBDSR); [2] Western Australian Register of Developmental Anomalies; [3] data based on the annual report (2012) published by the International Clearinghouse for Birth Defects, Surveillance and Research (ICBDSR); [4] Latin American Collaborative Study of Congenital Malformations; [5] not Reported; [6] for the details of the populations covered in each registry, please refer to the ICBDSR website at: <http://www.icbdsr.org>; [7] registries in this table are listed in alphabetic order.

not know for sure whether any change in these rates is due to a true existence/absence of epidemics in the region, due to the technical failure of our monitoring, or due to aetiologic and environmental teratogens. We do not have any parallel surveillance for environmental teratogens. The reasons behind the high/low rates of some groups of anomalies are still unclear. There need therefore for further investigations for every selected anomaly with unusual rate of occurrence in the area.

As a programme in a developing country, the condition of antenatal screening procedures, detection and ascertainment methods of defects, variable validity of the data, low coverage and small denominator population (due to the limited sources of funding), small number of cases (due to the small population covered), low power of the programme to find rare defects, and no full follow-up plan for anomalies after hospital discharge are still among the main limitations of the registry. The lack of epidemiological power and representativeness should therefore be carefully considered in examining the rates and patterns of various types of congenital anomalies, and when investigating for possible local causes and influencing factors of birth defects in the area.

For evaluation purposes, we assess the strengths and weaknesses of the TRoCA programme based on the major evaluation components of a standard monitoring system (i.e., simplicity, flexibility, acceptability, reliability, utility, sustainability, timeliness, sensitivity, and representativeness).

TRoCA has, so far, relied on staff for whom this programme was not their core duties. Allocating fully funded full time individuals for TRoCA may help to solve some parts of the above problems in its future activities.

It is concluded that as a small registry of congenital anomalies in a developing country, although TRoCA is still facing some challenges and problems, we believe that it has been successful in achieving its main objectives. Our experiences might be of interest and useful to practitioners, policymakers of birth defects control programmes, and mainly those willing to set up a monitoring system of congenital anomalies.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

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ORIGINAL PAPER

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Induced Abortion: a Systematic Review and Meta-analysis

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ABSTRACT

Background: Induced abortion accounts for 1 in 8 of approximately 600000 maternal deaths that occur annually worldwide. Induced abortion rate can be considered as one of the indicators for assessing availability of the appropriate reproductive health plans for women and identifying needs for appropriate related health policies and programs. **Material and Methods:** Researchers searched Pubmed, Google Scholar, CINAHL, Embase, PsycINFO, Cochrane, Iranian Scientific Information Database (SID), Iranian biomedical journals (Iranmedex), and Iranian Research Institute of Information and Documentation (Irandoc) between January 2000 and June 2013, which reported induced abortion. Search terms from two categories including abortion and termination of pregnancy were compiled. The search terms were "induced abortion" , "illegal abortion", "illegal abortion", "unsafe abortion", and "criminal abortion". The search was also conducted with "induced termination of pregnancy" ,"illegal termination of pregnancy"," illegal termination of pregnancy", "unsafe termination of pregnancy" and " criminal termination of pregnancy" . Meta-analysis was carried out by using OpenMeta software. Induced abortion rates were calculated based on the random effect model. **Results:** Overall induced abortion rate was obtained 58.1 per 1000 women (95% CI: 55.16-61.04). In continental level, rate of induced abortion was 14 per 1000 women (95% CI: 11-16). Nation-wide and local rates were obtained 67.27 per 1000 women (95% CI: 60.02-74.23) and 148.92 (95% CI: 140.06-157.79) respectively. **Discussion and Conclusion:** Induced abortion is a major public health problem that occurs worldwide whether under the legal restriction or freedom, and it remains as reproductive health concern globally. To eliminate the need for induced abortion is at the core of any effort for preventing this issue. Option with the highest priority is to prevent unwanted pregnancies through promoting reproductive health plans for women of reproductive age. In case the prevention strategies fail, universal provision of safe abortion services should be put in place.

Keywords: Induced Abortion, systematic review, meta-analysis.

1. INTRODUCTION

Induced abortion accounts for 1 in 8 of approximately 600000 maternal deaths that occur annually worldwide (1, 2) .

According to the WHO estimation, each year about 44 million induced abortions occur globally. About fifty percent of these abortions are unsafe, contributing substantially to maternal morbidity and approximately leading to 13 % of maternal mortality (3, 4) .

The induced abortion rate varies considerably. It was approximated 12 per 1000 women aged 15-44 years old in Western Europe, comparing to 43 in Eastern Europe (5). The induced abortion rate is even higher in countries like Uganda, where there were 54 induced abortions per 1000 women in 2003 (6). Evidence shows the induced abortions are more likely in countries in which abortion is illegal or restricted compared to those liberated (5). The majority (98 %) of unsafe abortions occur in developing countries with low level socio-economic state (1, 4, 7) . Induced abortion rate can be considered as one of the indicators for assessing availability of the appropriate reproductive health plans for women (5) and to identify needs for appropriate related health policies and programs (1). Aim of this study is to conduct a systematic review and meta-analysis on induced abortion rate worldwide.

2. METHODS

Inclusion criteria and search strategies

We searched PubMed, Google Scholar, CINAHL, Embase, PsycINFO, Cochrane, Iranian Scientific Information Database (SID), Iranian biomedical journals (Iranmedex), and Iranian Re-

search Institute of Information and Documentation (Irandoc) between January 2000 and June 2013, which reported induced abortion. We compiled search terms from two categories including abortion and termination of pregnancy. The search terms were "induced abortion" , "illegal abortion", "illegal abortion", "unsafe abortion", and "criminal abortion". The search was also conducted with "induced termination of pregnancy" ,"illegal termination of pregnancy", "unsafe termination of pregnancy" and " criminal termination of pregnancy". Results from the query were restricted to the publications in English and Farsi. Three reviewers independently screened the titles and abstracts of the retrieved papers to decide if they met the inclusion criteria for the meta-analysis. Any disagreement was resolved through consultation with the principal researcher. The form with predefined items was prepared and used for extracting data from the studies while reviewing the full text of the eligible studies. To be eligible for inclusion, the study had to report the abortion cases per pregnant women. The data collected for the analysis included: author name, study location, period of study, age range of the participants, the number of induced abortions, sample size, and confidence interval of the study.

We used the STROBE checklist to assess the quality of the studies. Studies evaluated as low quality were excluded from the systematic review and meta-analysis.

Heterogeneity of the studies was determined through deploying the Cochrane test ($p<0.05$) and quantified by I^2 statistic. Meta-analysis was carried out by using OpenMeta (8) version 12.11.14 which is completely open-source and cross platform software for advanced meta-analysis. Considering the heterogeneity of the studies, the random effect model (confidence interval= 95%) was applied for the analysis.

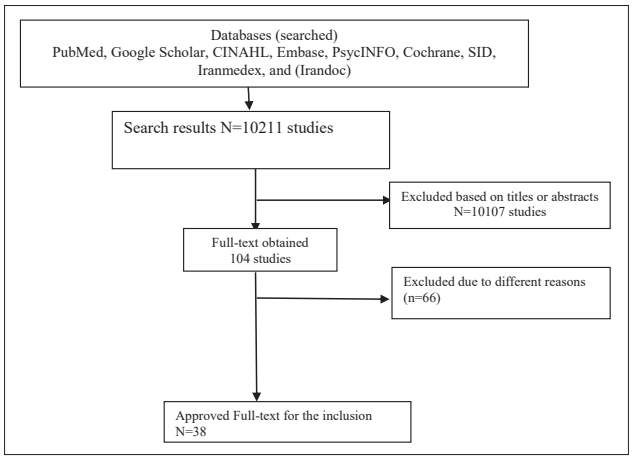

Figure 1. Flowchart of study selection

3. RESULTS

Description of studies

A total number of 38 studies were considered as a final list for the systematic review and meta-analysis. A total number of 67 statistics on induced abortion rate were extracted from the included studies. Sample size of studies was varied ranging from 43 to 1542857143. This variation was due to the various levels of the studies ranging from local level to the global scale. Table 1 shows induced abortion rates worldwide, nationwide and in the regional level.

I: to save the women life or prohibited altogether II: to preserve health III: Socioeconomic grounds IV: without restriction as to reason

Induced abortion rates in different levels

Abortion rate reported in the included studies ranged from 0.04 to 674.4.4 per 1000 the studied women. The lowest rate belongs to South Korea while the highest one is from Pakistan.

As it can be seen in Table 1, abortion rates are from different geographic levels including global, continental, national, regional or local levels. Four rates for induced abortion had been reported in global level. Twenty-one statistics had been related to continental level. Nineteen rates were reported on national level and 23 of them were in regional or local level. The remainders are in global level.

Majority of national rates (47%) belonged to the countries from Asia, followed by Africa (26%). There was only one statistic reported from European country, Romania, in national level. About 61 percent of the statistics reported in local or regional level were related to Asia, followed by those from Africa (21%) and Latin America (13%).

Overall meta-analysis of induced abortion rates

Figure 2 shows the results of meta-analysis conduced on all statisctics extracted from the studies. Overall abortion rate was 58.1 per 1000 women (95 % CI: 55.16-61.04). The lowest rate is related to the world in 2000, the second lowest one belongs to Vietnam and the third lowest rate belong to Indonesia.

Meta-analysis of induced abortion rates in different continents

Based on the random effect model, the overall abortion rate was 14 per 1000 fertile women, 95% CI (11 to 16). Substantial between-study heterogeneity was observed ($Q=36221823.84$, $df=20$, $I^2 = 10000$, $p\text{-value}<0.001$). Conducting Leave-one-out meta-analysis confirmed the validity and robustness of the meta-analysis. Figure 3 shows the result of this meta-analysis.

Meta-analysis of induced abortion rates in the national and local rates

As Figure 4 presents induced abortion rates for the local, regional and national levels were pooled from all 42 statistics and the summary rate of 101 per 1000 fertile women was obtained (CI=95%: 95-106 per 1000 fertile women). Cochrane's test shows high heterogeneity of the included studies ($Q=7028315$, $df=41$, $I^2=99.99$, $p\text{-value}<0.001$). Conducting one-leave-out meta-analysis also confirmed a large amount of heterogeneity.

Meta-analysis of induced abortion rates in different countries

Based on the random effect model, the overall abortion rate in national levels was 67.27 per 1000 fertile women (CI =95%:60.02 to 74.53). High heterogeneity was observed among studies ($Q=6992326$, $df=18$, $I^2 = 99.999$, $p\text{-value}<0.0001$). The validity and robustness of the meta-analysis was confirmed as the summary rate remained same after applying leave one out meta-analysis. Figure 5 shows the result of this meta-analysis.

Meta-analysis of induced abortion rates in different regions or cities

Based on the random effect model, the overall induced abortion rate in regional or local level was 148.92 per 1000 fertile women, 95% CI (140.06 to 157.79). High heterogeneity was observed among studies ($Q=25024.027$, $df=22$, $I^2 = 99.91$, $p\text{-value}<0.001$). Applying leave-one -out method of meta-analysis confirmed the result. Figure 6 shows the result of

Study Location	Abortion Law status	Continent	Study Period	Age range	Population Size	Induced Abortion Rate(per 1000 fertile women)	Scope	Lower CI	Upper CI
Rwanda (7)	II	AF	2009	15-44	2407652	25.04	National	24.8	25.23
Mexico(9)	I	LA	1999-2006	15-44	26515152	33	National	32.9	33.1
Peru(10)	II	LA	2005(Sep-Dec)	18-29	7992	116.12	National	109	123
Ethiopia(11)	II	AF	2008	15-44	16608696	23	National	22.9	23.07
Pakistan-1(12)	II	AS	2002	15-49	30689655	29	National	28.9	29.06
Guatemala-1(13)	I	LA	2003	15-49	2708333	24	National	23.8	24.18
Uganda-1(6)	I	AF	2003	15-49	5500000	54.1	National	53.81	54.19
Philippines(14)	I	AS	2000	15-44	17533333	27	National	26.92	27.08
Burkina Faso(15)	II	AF	2008	15-49	3488000	25	National	24.84	25.16
South Korea(16)	II	AS	2005	15-44	11491040	0.04	National	0.03	0.05
Vietnam(17)	IV	AS	2001	15-49	27097	400	National	394	406
Romania(18)	IV	EU	2001	15-49	500	32	National	16.6	47.43
Cambodia(19)	IV	AS	2005	16-53	3644327	8.6	National	8.5	8.7
Indonesia(20)	I	AS	2000	15-49	54054054	366.7	National	366.3	367.1
Uganda-2(21)	I	AF	2002	15-44	5182926	16.4	National	16.3	16.5
Pakistan-2(21)	II	AS	2002	15-44	28142857	7	National	6.97	7.03
Guatemala-2(21)	I	LA	2003	15-44	2511627	86	National	85.65	86-35
Philippines(21)	I	AS	2000	15-44	17761363	4.4	National	4.37	4.43
Iran(22)	I	AS	2000	15-49	9760000	7.47	National	3.135	6.406
Abbottabad(23)	II	AS	2006-2007	20-45	1090	47.7	Local/Regional	35.05	60.36
Bavi district in Vietnam(24)	IV	AS	1999-2004	15-44	5259	139.4	Local/Regional	130.02	148.74
Athens- Greece(25)	IV	EU	2005-2008	Above 39 years	163	380.37	Local/Regional	305.84	454.9
Edo State- Nigeria(26)	I	AF	2002	15-24	601	409.32	Local/Regional	370.01	448.63
Berekum District-Ghana(27)	II	AF	1999(Jan-Feb)	15-49	1685	473.59	Local/Regional	449.75	497.43
Rural South India(28)	III	AS	1996	15-45	283	183.75	Local/Regional	138.62	228.87
Kargera Region(Urban)-Tanzania(29)	I	AF	2006	Under 24 years	473	625.79	Local/Regional	582	669.4
Temeke Municipal Hospital(Rural)-Tanzania(29)	I	AF	2003	Under 24 years	278	622.3	Local/Regional	565.3	679.2
Bahawalpur-Pakistan(30)	II	AS	2008	15-44	2500	8.4	Local/Regional	5	12
Hyderabad-Pakistan(31)	II	AS	2008(March)-2009(Feb)	15-44	230	217.4	Local/Regional	164.1	270.7
Lusaka- Zambia(32)	III	AF	2005(4-month period)	13-19	87	390.8	Local/Regional	288.3	493.3
Cartagena-Columbia(33)	II	LA	2005	15-44	9950	221.2	Local/Regional	213.05	229.36
Cartagena-Columbia(33)	II	LA	2006	15-44	9509	221	Local/Regional	213	229
Cartagena-Columbia(33)	II	LA	2007	15-44	9377	209.9	Local/Regional	201.7	218.2
Karachi- Pakistan(34)	II	AS	2005-2009	18-42	43	674.4	Local/Regional	534.4	814.4

Tehran, Iran(35)	I	AS	2008	15-44	2098790	5.49	Local/Regional	5.39	5.59
Tehran, Iran(36)	I	AS	July 2003- Jan 2004	15-55	2470	94.33	Local/Regional	83	106.9
Tehran, Iran(35)	I	AS	2009	15-44	2934	5.45	Local/Regional	2.78	8.11
Isfahan, Iran(37)	I	AS	2003-2004	15-50	417	119.9	Local/Regional	88.72	15.11
Shiraz, Iran(38)	I	AS	2001	15-49	550	29.09	Local/Regional	15.04	43.13
Kermanshah, Iran(39)	I	AS	2004	NOS	11206	1.34	Local/Regional	0.66	2.01
Tehran, Iran(40)	I	AS	1991-1995	102	1115	91.4	Local/Regional	74.5	108.4
Kermanshah, Iran(41)	I	AS	1992-2002	NOS	205250	64.99	Local/Regional	63.9	66.06
Africa-1(1)	Mostly I,II, Some III,IV	–	2003	15-44	189655172	29	Continental	28.9	29.02
Asia-1(1)	I,II,III,IV	-	2003	15-44	890909091	11	Continental	10.9	11.01
Europe-1(1)	Mostly IV Some III and II	-	2003	15-44	166666667	3	Continental	2.99	3.01
Latin America-1(1)	I,II Few IV	-	2003	15-44	134482759	29	Continental	28.9	29.03
North America-1(1)	IV	-	2003	15-44	71428759	0.7	Continental	0.69	0.71
Oceania-1(1)	IV	-	2003	15-44	6666667	3	Continental	2.9	3.04
Africa-2(42)	Mostly I,II, some III,IV	-	2000	15-44	190909091	22	Continental	21.98	22.02
Asia-2(42)	I,II,III,IV	-	2000	15-44	954545455	11	Continental	10.99	11.01
Europe-2(42)	Mostly IV Some III and II	-	2000	15-44	166666667	3	Continental	2.99	3.01
Latin America-2(42)	I,II, Few IV	-	2000	15-44	142307692	2.6	Continental	2.59	2.61
Oceania-2(42)	IV	-	2000	15-44	2000000	15	Continental	14.83	15.17
Africa-3(4)	Mostly I,II, some III,IV	-	2008	15-44	221071429	28	Continental	27.98	28.02
Europe-3(4)	Mostly IV Some III and II	-	2008	15-44	180000000	2	Continental	1.9	2.01
Asia-3(4)	I,II,III,IV	-	2008	15-44	980000000	11	Continental	10.99	11.01
Latin America-3(4)	I,II, Few IV	-	2008	15-44	136451613	31	Continental	30.97	31.03
Oceania-3(4)	IV	-	2008	15-44	2250000	8	Continental	7.88	8.12
Africa-4(5)	I,II,III,IV	-	2008	15-44	194482758	28	Continental	27.98	28.02
Asia-4(5)	I,II,III,IV	-	2008	15-44	975000000	11	Continental	10.99	11.01
Latin America-4(5)	I, II, Few IV	-	2008	15-44	133333333	31	Continental	30.97	31.03

Europe-4(5)	Mostly IV Some III and II	-	2008	15-44	155555555	2	Continental	1.99	2.01
Oceania-4(5)	IV	-	2008	15-44	5882352	2.95	Continental	2.91	2.99
Worldwide-1(1)	I,II,III,IV	-	2003	15-44	1407142757	14	Global	13.99	14.01
Worldwide-2(42)	I,II,III,IV	-	2000	15-44	1583333333	75.16	Global	75.14	75.17
Worldwide-3(4)	I,II,III,IV	-	2008	15-44	1542857143	14	Global	13.99	14.01
Worldwide-4(5)	I,II,III,IV		2008	15-44	1564285714	14	Global	13.99	14.01

Table 1. Basic description of statistics extracted on induced abortion rates

meta-analysis.

Meta-analysis of induced abortion rates from Iran

Based on the random effect model, the overall abortion rate for Iran was 26.84 per 1000 fertile women, (CI=95%:23.1 to 30.58) (Figure 7). Large amount of heterogeneity existed among statistics reported from Iran (Q=13147, df=8, I^2 = 99.94, p-value<0.00001).

4. DISCUSSION

This meta-analysis shows the induced abortion rate per 1000 fertile women (aged 15-45/49) in global, continental national and local/regional level. The results revealed the high heterogeneity among different regions across the world. Midpoint induced abortion rate from 67 included statistics was 58.1 per 1000 women (13-49 years old). Overall meta-analysis revealed that the global rate of induced abortion in 2000 as the lowest followed by the national induced rate reported for Vietnam in 2001, and the national rate for Indonesia. Asia in 2008 had the highest rate of the induced abortion in global scale meta-analysis. These findings are in accordance with the achievement of population and family strategy in mid-2000 in Vietnam (43). Vietnam is among the countries with completely liberal abortion law (44). The fact that induced abortion is highly restricted in Indonesia and such practice is a criminal offence and accordingly all abortion cases are officially announced as the spontaneous abortion may explain to some degree the position of this country in forest plot (45). In this context, it makes sense when some consider abortion as "confused challenge to the public health and legal systems of Indonesia" (46) .

Looking at forest plot of induced abortion in continental level, it is evident that Africa and Latin America have similarity. Asia in 2000, 2003, and 2008 has been nearly overlapped with the summary line. Based on the meta-analysis, Europe and Latin America have been located in the same position in 2000 while the Latin America has moved in opposite side in 2003 and 2008. This may be attributed to the major changes happened in the region after 2000. For instance, Portugal reformed their abortion law significantly in 2007 while it was more restrictive earlier. Similarly, Switzerland made the abortion law more liberated in 2002. In addition, France extended the gestational period during which the abortion is legal and made the abortion more accessible. Denmark and Sweden also removed restriction of non-residents for accessing to abortion in these countries (47).

Meta-analysis in the national level highlighted the difference of Indonesia and Vietnam with others. Looking at the national level analysis, Indonesia appears to be a specific case and its situation remains similar in both global and national meta-analysis. This country is among those with highly restricted abortion law. Compared with the global level, the position of Vietnam has moved closer to the Indonesia in the national level analysis. In contrast with Indonesia, Vietnam has completely liberal abortion law. This implies there might be no association between the legality of abortion and its incidence.

Although, Indonesia, Vietnam, and Philippines from Asia and Peru from Latin America all are at the same side of the summary line, Philippines and Peru are relatively close to the summary line.

Based on of meta-analysis in regional or local level, it is evident that abortion rate of Rural Vietnam has overlapping with the summary line in forest plot. Iranian Cities (except for one from Kermanshah), Abbottabad and Bahawalpur from Pakistan have been located in left side of the summary line. Other cities have been located in opposite side of the summary line. Moreover, Tehran in 2008 has the highest rate in the plot and it appears to have similar situation with Bahawalpur from Pakistan.

High heterogeneity observed among different locations can be justified with socio-demographic, socioeconomic, or even socio-cultural characteristics of those places or changes in these characteristics. In addition, this heterogeneity might be originated from the differences in reporting induced abortions rates and its reliability due to different laws, beliefs, religion, ideologies, norms, or ethical principles in different places. For instance, childbearing outside of wedlock is not acceptable or legitimate in some societies while it is acceptable in others. Variety of data sources can also be another cause of the heterogeneity (48, 49) .

Changes in view of women on the family size, economic pressures, late marriage, access to population and family planning services including providing population with appropriate education, lack of appropriate social policies for promoting a mother and child friendly society as well as the women quest for achieving social and economic equality by woman can also influence the induced abortion rate (50-52).

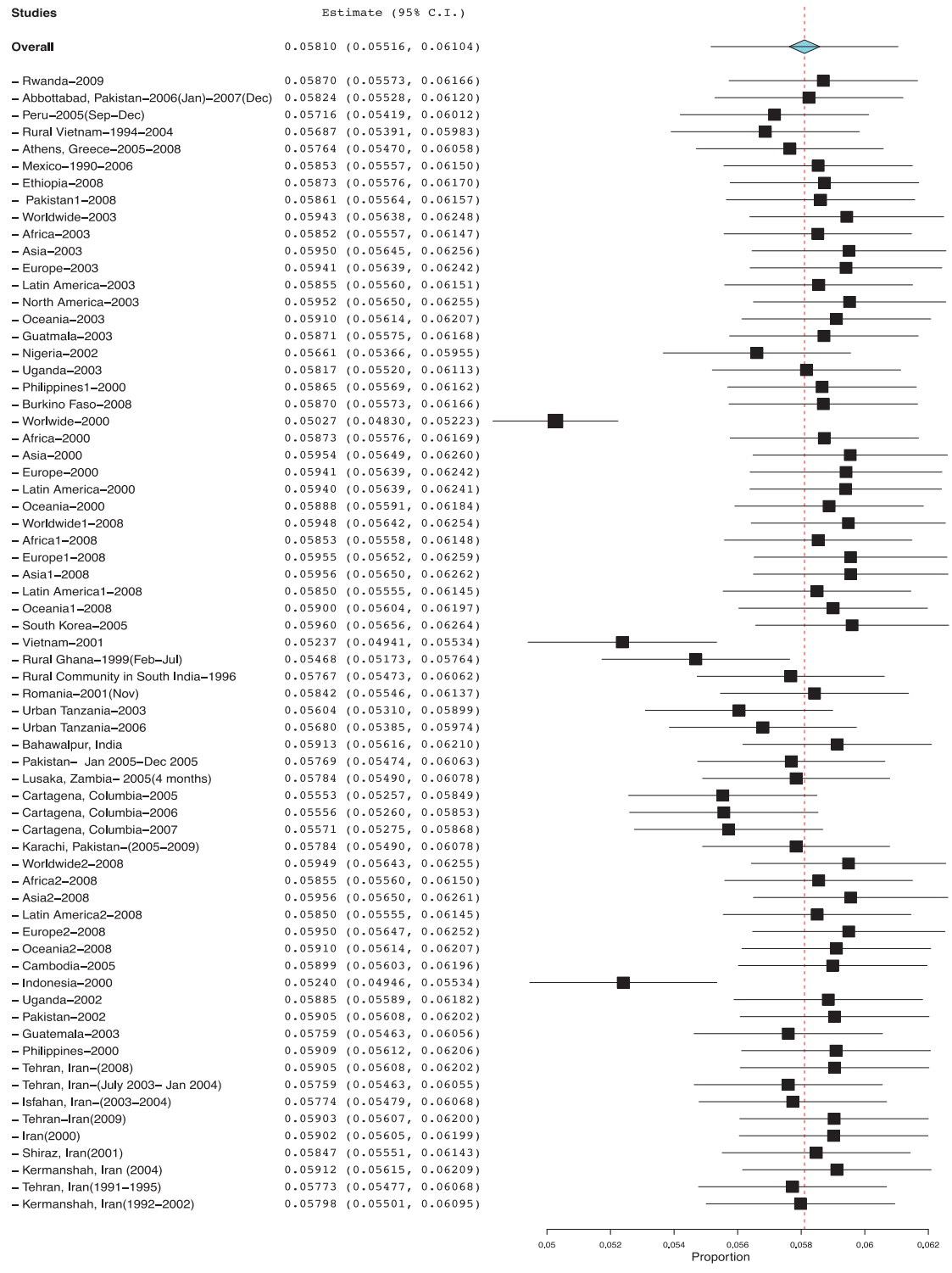

Figure 2. Meta-analysis of overall abortion rates based on random effect model

5. CONCLUSION

Induced abortion is a major public health problem that occurs worldwide whether under of legal restriction or freedom, and it remains as reproductive health concern globally. To eliminate the need for induced abortion is at the core of any effort for preventing this issue. Regardless of the region, availability of appropriate choices for women in reproductive age is vital. Policies should support these choices and authorities should put appropriate and effective mechanisms in place to make these choices feasible. The first high propriety

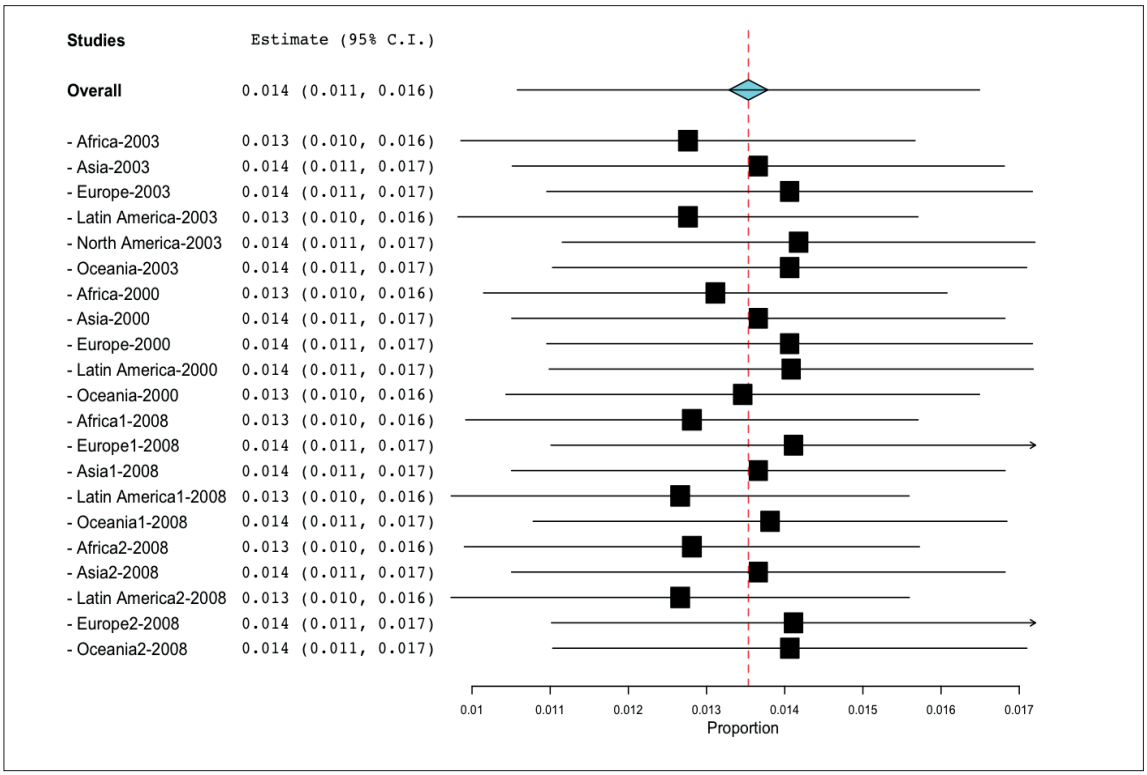

Figure 3. Meta-analysis of abortion rates in Continental level based on random effect model

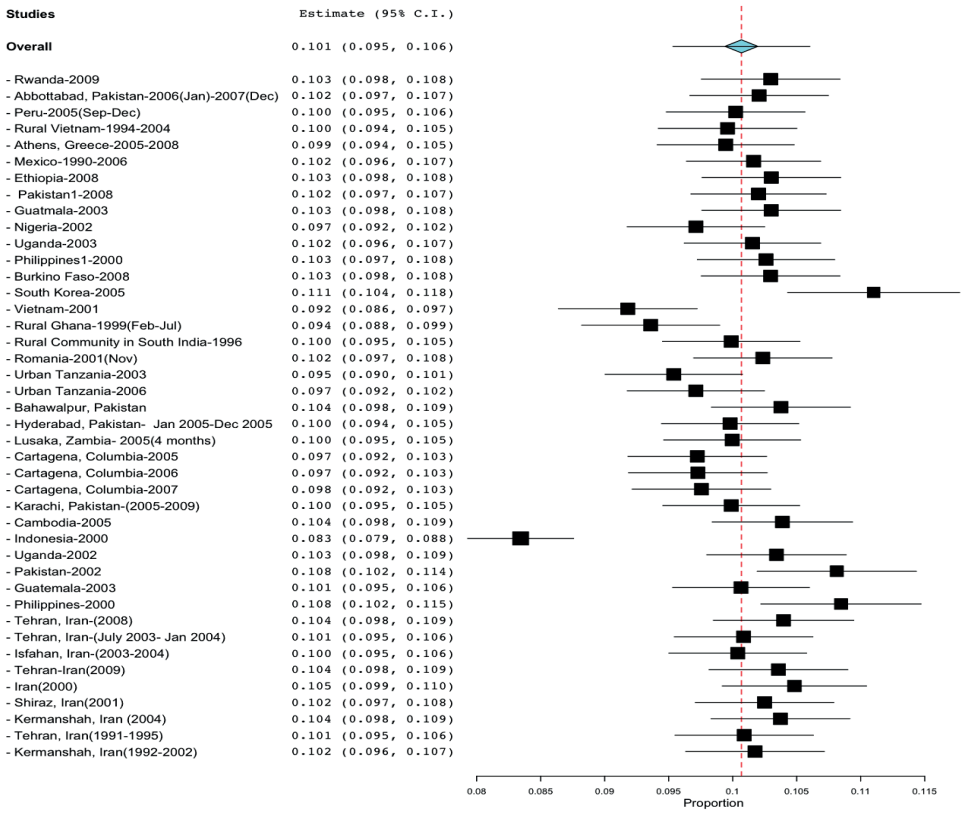

Figure 4. Meta-analysis of abortion rates in National and Local level based on random effect model

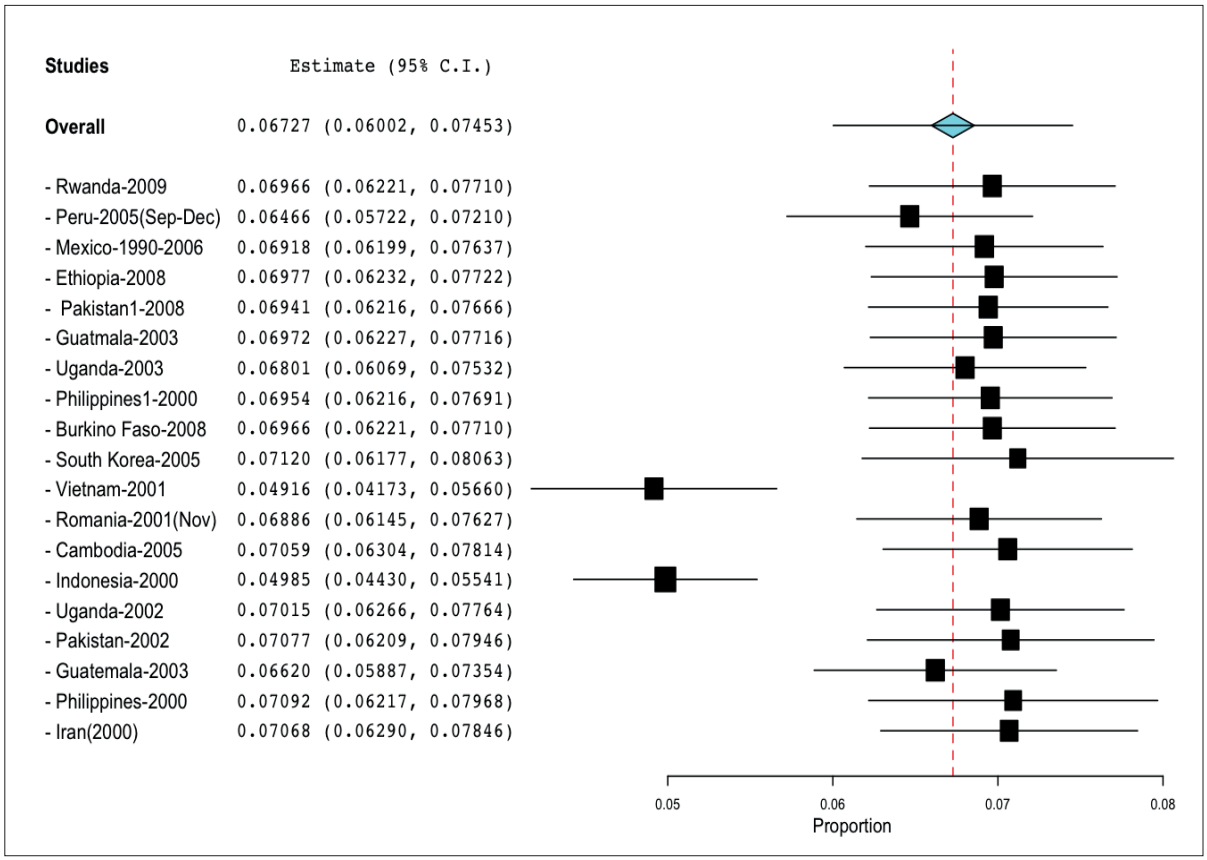

Figure 5. Meta-analysis of the abortion rates in National level based on random effect model

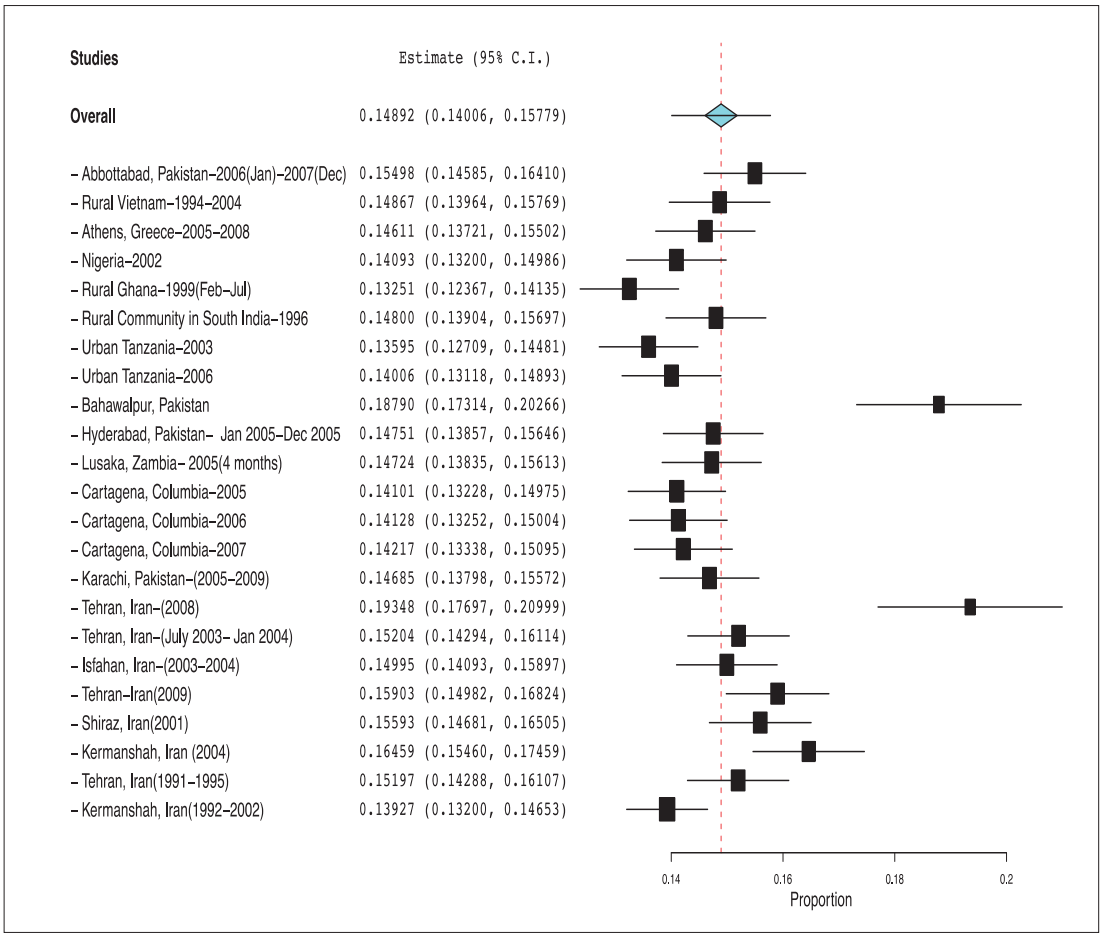

Figure 6. Meta-analysis of abortion rates in regional or local level based on random effect model

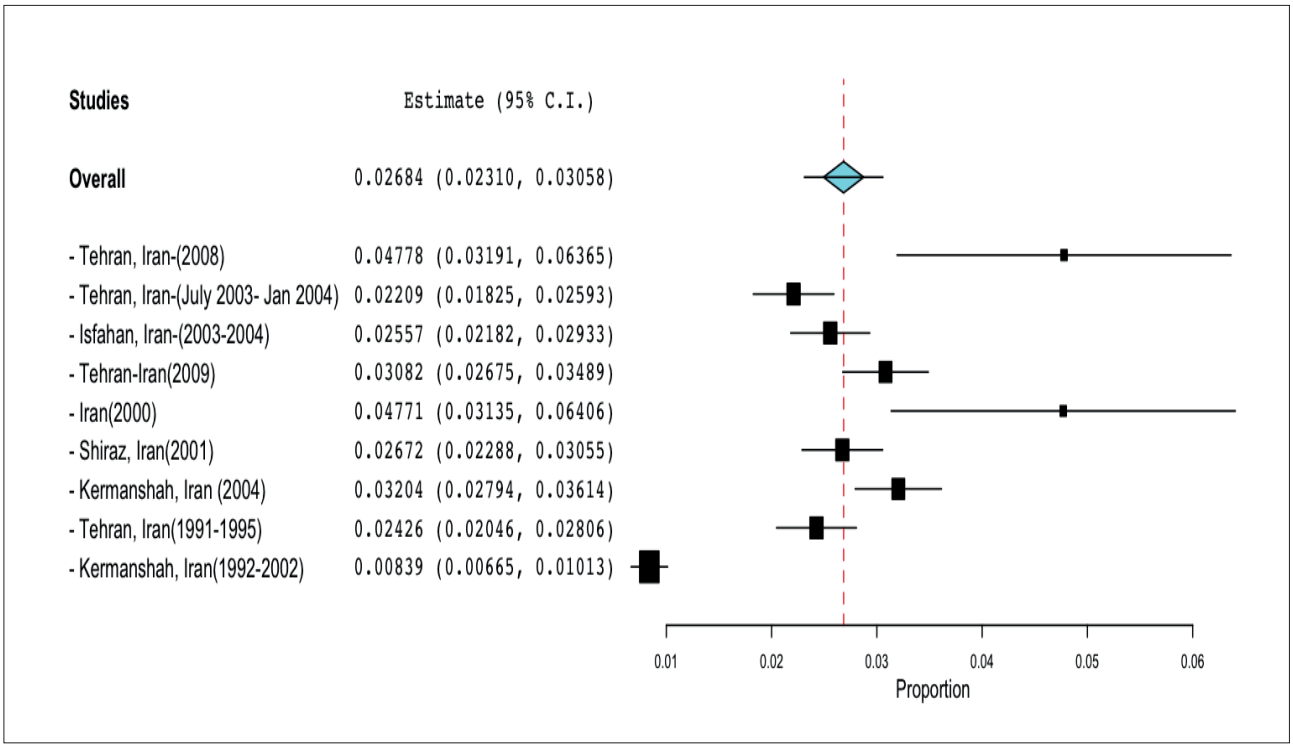

Figure 7. Meta-analysis of abortion rates in Iran based on random effect model

option should be to prevent unwanted pregnancies through educational and contraceptive interventions. The second high priority is timely and easy provision of safe abortion services for all those with unintended pregnancy.

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ORIGINAL ARTICLE

Reliability and validity of the March of dimes preconception/prenatal family health history questionnaire: The Persian version

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ABSTRACT **In recent years, there has been a remarkable gap between rapid advancements in genetic technology and public health practice. Looking at the familial health history may bridge this gap for easier and cheaper diagnosis and prevention of congenital anomalies.The aim of this study was to validate and culturally adapt the March of Dimes Preconception/Prenatal Family Health History Questionnaire for the Iranian population.After obtaining written permission from March of Dimes, the translation–back translation of the original questionnaire was performed. The content validity was assessed by a team of 12 experts. Based on a sample of 50 general practitioners and 100 subjects referred to health centers from September to November 2014 in Tabriz, Iran, test-retest reliability and inter-rater reliability were evaluated by Kappa and Intra-class Correlation Coefficient (ICC). Content validity of the Persian version of the questionnaire was confirmed according to the modified kappa value above 0.76 for all the items included in this tool. Inter-rater reliability assessment yielded a kappa value between 0.62 and 0.92 for variables with dichotomous measurement scales and ICC ranged from 0.6 to 0.9 for variables with numeric scales. Test–retest re-administration produced kappa ranging from 0.62 to 0.92 for variables with dichotomous measurement scales and ICC from 0.6 to 0.9 for variables with numeric scales. The Persian version of the March of Dimes preconception/prenatal family health history questionnaire showed acceptable reliability and validity and may be used as a simple tool for the detection of risk factors of birth defects in Iranian population.**

Key Words: family history, questionnaire, reliability, validity

INTRODUCTION

"Congenital anomalies affect 1 in 33 infants with 3.2 million birth defect-related disabilities every year in the globe. They may result in long-term disability with significant impacts on individuals, families, health care systems and communities" (WHO 2014). Birth defects are the first leading causes of prenatal mortality and childhood morbidity and disability in many countries (Dastgiri et al. 2011). A recent report by the March of Dimes showed that, worldwide, an estimated 6% of births or 7.9 million children are born annually with a major birth defect of genetic or partially genetic origin (Romitti 2007). Congenital anomalies are the most common causes of death in children (1–59 months) in Iran (Rahbar et al. 2013). Total prevalence of congenital anomalies was 1.9 per 100 births between 2000 and 2011 in east Azerbaijan, northwest of Iran (Bateni et al. 2013).

"The wide range of causes of birth defects means that a portfolio of prevention approaches is needed. The prevention of these disorders is available in 60% of cases" (Czeizel 1993; Czeizel et al. 1993).This needs however epidemiological information.

Genetic achievements can be applied to public health programs by taking family history, even though the advent of genomics and consequently its domination challenged us to examine how we can apply the assumptions of genetic knowledge to public health practice (Khoury 2003). Meanwhile, such a big challenge can also serve as an opportunity to target health promotion activities to high risk populations in a more effective and efficient manner. Thus, family health can be regarded as a unique tool to grab this opportunity because it covers such genetic and environmental components of the diseases as shared cultural and behavioral risks. (Khoury 2003; Yoon et al. 2003).

The Centers for Disease Control and Prevention (CDC) in their 2006 report offered 10 recommendations for improving preconception health. One of the elements of these recommendations is obtaining preconception family health history (Johnson et al. 2006).

Family history can also lead to early diagnosis during pregnancy, which allows for secondary interventions in decision-making during pregnancy, including location and mode of delivery and tertiary interventions in medical care during the newborn period and childhood (Dolan and Moore 2007).

Various tools for assessing preconception family health history have been developed and validated but there is currently no validated instrument designed specifically for Iranian people focusing on birth defects.

The aim of this study was to validate and culturally adapt the March of Dimes Preconception/Prenatal Family Health History Questionnaire for the Iranian population.

MATERIALS AND METHODS

Subjects

This study was carried out in the Tabriz district, in the northwest of Iran. The study consisted of 100 married female subjects who were recruited from a rural population of the Tabriz district and referred to health centers from September to November 2014. Rural population in the region was 158 731 people who received their primary health care from 17 health centers. The inclusion criteria included married female populations, aged 15–49.

Using Microsoft Excel 2010 eligible persons were selected randomly. Each woman had a unique code in the rural health care system.

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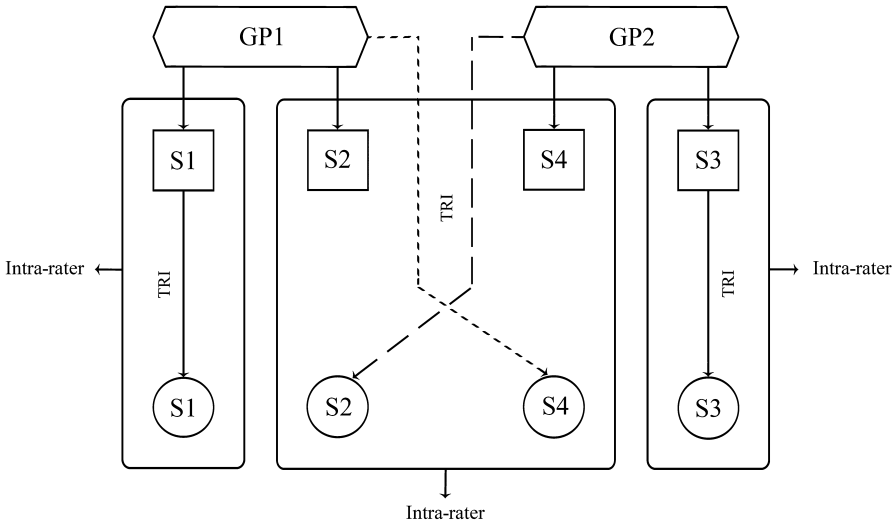

Fig. 1 Allocation diagram for assessing inter-rater and intra-rater reliability of the questionnaire.
GP, General Practitioner; S, Subject; TRI, Test Retest Interval = 4 weeks.
□, Test phase; ○, Retest phase.

All 50 general practitioners (GPs) who worked in rural health centers of the Tabriz district were invited to participate in this study to complete the questionnaires for the subjects. These GPs were grouped randomly to 25 pairs. Each pair of GPs was randomly allocated to assess four subjects who were randomly selected from the 100 sample participants. As illustrated in the Figure 1, the questionnaire was completed for all four subjects twice with the time interval of 4 weeks. Both two phases of administration and re-administration of the questionnaire were performed by the same GPs in the paired group for two subjects in order to assess intra-rater reliability. To investigate inter-rater reliability the re-administration phases were performed independently by both the GPs for two remaining subjects of the group (dashed lines in Figure 1). The duration of each data collection was approximately 15–20 min. All data were collected during a 2-month period in 2014. Neither the physicians nor the study subjects knew about the second interview in advance.

Selection of the questionnaire

We reviewed the literature to find the birth defects-specific tool for obtaining preconception family health history. Among methods such as Becoming a Parent, 2nd Edition–Wisconsin Association for Perinatal Care (Committee, 2007), Comprehensive Perinatal Services Program–Initial Combined Assessment, California (Program, n. d.), Women's Health Questionnaire–Boston Healthy Start Initiative (Commission, n. d.), PKC Preconception Guidance Tool (Tool 2006), The Preconception/Prenatal Family History Questionnaire–The March of Dimes (Foundation, 2008), met all of the requirements. We got permission from the Associate Director, Health Information Delivery Pregnancy & Health Education Center of March of Dimes Foundation to start the validation study of this tool.

Measurements

This tool was initially designed by March of Dimes as a highly valid and reliable measure of preconception family health history. The tool was designed for use in the clinical care setting to screen for potential risks of families associated with birth defects.

This checklist was developed to gather information about the married women and their spouses. The questions cover basic demographic information, ethnic background, past medical and developmental history, and current medical issues, exposure to risk factors and health behaviors for both the wife and her spouse. The questionnaire also includes data such as number of pregnancies, number of full-term and preterm births and number of stillbirths, we labeled this section as "pregnancy background". It also includes past medical history of particular diseases, for example, thyroid diseases, diabetes and seizures, which were referred to as "particular diseases history". A wide range of specific conditions about couples and their extended families are covered through the past medical and developmental history section. Two more questions include having had a genetic testing and being blood relatives of couples, which we considered as the category of "others".

A small space for "office use only" was replaced in the tool to write significant findings and recommendations as well as the date discussed with family, the health care provider's signature, and the patient signature.

Preparation of the Persian versions

The English version of the questionnaire was translated into Persian by two bilingual experts providing the first draft of the Persian version of the instrument after reaching dual agreement on the translation of English text. The ethnic background items changed totally according to the existing ethnic groups of the Iranian population. The draft was then checked by an expert panel of two pediatricians, one epidemiologist and an obstetrician. The Persian translation agreed by the expert panel was then back-translated into English by another bilingual person and was compared for compatibility with the original version.

Content validity

The content validity was assessed by a team of 12 professional experts including pediatricians, gynecologists, obstetricians, public health practitioners and clinical geneticists. In the qualitative assessment, experts provided written feedback on the clarity and relevance of the content of the questions to the Iranian culture. To ensure valid applicability and prevent loss of reliability due to potentially various understandings of the items in different cultural settings, a process of cultural adaptation was followed through investigating and discussing all the items in a panel of experts and making modifications or adding descriptions to those items needing to be clarified or explained. For instance, the ethnic background items were substituted by an existing ethnic group of the country. A

brief description was provided for the questions related to specific medical conditions such as Canavan disease, Phenylketonnuria, Gaucher disease by a team of professional experts. Quantitative evaluation was performed by administering a questionnaire for each expert panel to ask the necessity, relevancy, simplicity and clarity of each item based on a 4-point scale response to each question.

Ethical considerations

All eligible subjects were asked to complete written informed consent to participate in the study. All subjects' information remained confidential. This survey received ethics approval from the committee of ethics in Tabriz University of Medical Sciences.

Statistical analysis

The content validity statistic used in this study was the modified content validity index (modified kappa). This index is preferred to traditional I-CVI because it also measures the chance agreement (Polit et al. 2007).

The reliability for variables with dichotomous measurement scales such as past medical and developmental history was assessed using kappa statistic (Sim and Wright 2005). Kappa values of 0.80 and above represented excellent agreement, values between 0.61 and 0.80 represented substantial agreement, 0.41 to 0.61 represented moderate agreement, and values below 0.40 suggested fair to poor agreement (Landis and Koch 1977). The Intra-class Correlation Coefficient (ICC) was used to assess the reliability for variables with numeric scales such as pregnancy background. ICCs ≤ 0.4 were considered poor to fair, 0.41–0.60 moderate, 0.61–0.80 good and >0.80 excellent (Bartko 1966).

Data were analyzed using the STATA 11 statistical software package (STATA Corporation, College Station, TX, USA).

RESULTS

Sample characteristics

A total of 190 completed questionnaires were collected for data analysis, with less than 5% missing data. The mean age of participants was 32.4 (SD = 10.3). Seventy-four subjects had an under diploma education (74%), few had finished high school (total 10 persons and 10%) and 16 (16%) subjects were illiterate. Eighty-three persons were housekeepers without an income and 17 worked as carpet weavers with an income level of less than $US200 per month.

Mean age of the GPs who completed the questionnaires for subjects was 37 (SD = 5). Thirty-three GPs (66%) were female and 17 (34%) were male. Mean length of working experience of GPs in the health centers was 8 years (SD = 3).

Content validity

The content validity of the questionnaire was assessed by a team of 12 professional experts. Except for few minor changes, no major change was applied to the original instrument. From the first step of the assessment of the tool, five items of the 134 questions were revised according to the quantitative evaluation and qualitative recommendations of the experts. Content validity of the Persian version of the questionnaire was confirmed according to the modified kappa value above 0.76 for all items included in the tool.

Intra-rater reliability

For the intra-rater component of the study, questionnaires were administered and re-administered for 96 subjects with the time interval of 4 weeks. Across the items with dichotomous measurement scales, kappa varied between 0.68 and 0.94. Table 1 presents intra-rater reliability for various category of the questionnaire.

Test-retest reliability for the category of pregnancy background was assessed using the intra-class correlation coefficient, which ranged from 0.74 for "Miscarriages" and "Preterm labor" to 0.96 for "Number of Pregnancies". Sixty-seven percent of the items of the pregnancy background category yielded excellent agreement and the remaining 33% yielded good agreement.

Inter-rater reliability

As expected, inter-rater agreement measures were slightly lower than those for intra-rater agreement which were calculated for 94 questionnaires. As indicated in Table 1, kappa values showed substantial to excellent agreements across the items with dichotomous measurement scales ranging from 0.62 to 0.92.

Inter-rater agreement was then examined for variables with numeric scales through pregnancy background category using ICC. Fifty-five percent of items had ICC values greater than 0.8, showing that inter-rater agreement was excellent and 45% ones produced ICC over 0.61, suggesting that inter-rater reliability was good.

DISCUSSION

"Obtaining a family history remains an inexpensive and basic approach to identify individuals at risk for genetic disorders. Family history is a way to reach those at higher risk and to target resources to get them into screening. A family history can establish patterns of

Table 1 Inter-rater and intra-rater reliability statistics for the various categories of the questionnaire

	Inter-rater reliability (Kappa)			Intra-rater reliability (Kappa)		
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Category (number of items)	≥0.80	0.61–0.80	≤.60	≥0.80	0.61–0.80	≤0.60
Past medical history (8)	6 (75)	2 (25)	0	7 (87)	1 (13)	0
Ethnic background (2)	2 (100)	0	0	2 (100)	0	0
Health behaviors (10)	7 (70)	3 (30)	0	8 (80)	2 (20)	0
Particular diseases history (11)	5 (45)	6 (55)	0	7 (64)	4 (36)	0
Exposure to risk factors (4)	3 (75)	1 (24)	0	2 (50)	2 (2)	0
Past medical and developmental history of families (74)	52 (70)	22 (30)	0	61 (82)	13 (18)	0
Others (7)	6 (86)	1 (14)	0	5 (71)	2 (29)	0

inheritance and serve as a guide to diagnostic, therapeutic, and preventive approaches" (Malarcher et al. 2002). In this study, we aimed to evaluate the validity and reliability of the March of Dimes Preconception/Prenatal Family Health History Questionnaire for the Iranian population. According to the findings of this study, the Persian version of the questionnaire showed good content validity and sufficient comprehensiveness. The data of the study also proved that the results were replicable over a 4-week period.

To our knowledge, reliability and validity of this tool have not been examined yet in Iran and other countries; therefore, data collected through this study were not comparable with similar studies.

In terms of comprehensiveness, according to the feedback given by the close scrutiny of 12 professional experts and their remarkable approval of the validity variables, it can be inferred that the questionnaire includes the critical and essential points to investigate risk factors for birth defects. The relevancy and clarity criteria were also verified by the reviewers with the expression that all items could be understood clearly without any unnecessary questions included. To assess the content validity based on the expert views, a traditional consensus-based content validity index is being used in most studies. However, we used an alternative modified measure that takes into account the consistency of agreements (Polit et al. 2007).

Intra-class correlation coefficients for numeric variables and kappa statistics for dichotomous variables showed acceptable test-retest reliability and inter-rater reliability for the questionnaire items. The majority of items (92 of 116, 80%) had kappa values greater than 0.8 and 20% of items showed kappa between 0.61 and 0.8, suggesting that intra-rater agreement was substantial to excellent for variables with dichotomous measurement scales. ICC for variables with numeric scales ranged from 0.74 to 0.96 indicating good to excellent test-retest reliability. Inter-rater reliability also was promising, which yielded kappa between 0.62 and 0.92 for variables with dichotomous measurement scales and ICC ranged from 0.6 to 0.9 for variables with numeric scales.

Considering the role of screening programs in the prevention of birth defects especially in the developing countries such as Iran indicates the necessity of applying them in their health system. Accordingly there is a need for a valid and reliable tool to set up a prevention program for congenital anomalies in Iran. Iran has a very efficient and potential primary health system network that has recently been more activated by applying the "Family Physician" project. So there is a sufficient opportunity to design a surveillance system for congenital anomalies. A valid and reliable questionnaire as a risk assessment tool can play a key role in early detection of birth defects in such a surveillance system.

The Persian version of the March of Dimes preconception/prenatal family health history questionnaire showed acceptable reliability and validity and may be used as a simple tool for the detection of risk factors of birth defects in the Iranian population.

Some points should be taken into account about the application of this tool.

The March of Dimes Preconception/Prenatal Family Health History Questionnaire is a risk assessment tool. As a risk assessment tool, the use of such a questionnaire will be helpful for increasing the chance of detecting those at higher risks of genetic disorders (Frezzo et al. 2003); however, some limitations should also be considered, such as the fact that this tool has not been validated and widely used over various settings or populations worldwide and its real value is not well documented. No doubt cost-effectiveness needs also to be assessed before recommending its use widely. In this research study we only assessed the validity and inter- and intra-rater reliability of this tool in the study setting. So applicability of this questionnaire in the whole population of the country needs to be investigated in other cost effectiveness studies.

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DISCLOSURE

None.

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ORIGINAL PAPER

Minimum Data Set for Cystic Fibrosis Registry: a Case Study in Iran

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ABSTRACT

Background: over the last 25 years several national registries of CF have been set up. Such systems can be very useful in providing an integrated resource for improving patient care and conducting research on the disease. Minimum Data Set is a common set of data items that should be used to collect and report data in the registry. The principal aim of this research was to determine minimum data set for the CF registry in north-west of Iran. **Methods**: data items collected by several selected registries of cystic fibrosis were studied and an initial set of data was selected by the researchers. A group of experts including epidemiologists, pediatricians, and CF specialists were asked to review the proposed data elements and score them based on their importance by using a nine-point Likert scale. The items scored as important or highly important by more than 50 % of the experts, were included in final list of minimum data set. Availability of data was evaluated through reviewing medical records of 144 patients hospitalized in Children Hospital located in Tabriz. **Results**: overall six classes of data (46 items) were identified in the selected registry systems for cystic fibrosis: patient demographics, administrative data, survival status, diagnostic procedures, genetic and clinical manifestations, and therapeutics. Thirty two data elements from all six categories of data were approved by the experts as the minimum data set for cystic fibrosis registry system. Availability of data in administrative category and survival class was 100 percent. Collecting data on medications was feasible in 100% of the cases as well. In class of demographic data, accessibility of patient name, age, gender, place of birth, and date of birth was 100 percent. In group of diagnostic procedures, partial availability of data was found for sweat test and genetic test. No data was found on the antenatal screening, exercise tolerance test, and glucose tolerance test. **Conclusion**: this work can be considered as a first step toward establishing CF registry system in Iran. Minimum data set can be also useful in designing electronic registry or electronic patient records for those suffering from CF toward integration of their fragmented records across continuum of the health care system in order to improve quality of shared patient care.
Keywords: minimum data set, registry, data elements, cystic fibrosis, and core data set.

1. INTRODUCTION

Cystic fibrosis is an autosomal recessive disease and a hereditary disease of mucus and sweat glands caused by a CF transmembrane regulator defect that mainly affects the respiratory and gastrointestinal systems, leading to progressive disability (1, 2). According to WHO, 1 in 2000-3000 newborns is affected by CF across the Europe; in north America the incidence has been reported to be 1 in 3500; no accurate data are available in Africa; in middle east various incidence rates have been reported ranging from 1 in 2560 to 1 in 15876 (3). However these statistics differ from country to country. For example the incidence reported for Ireland, UK, Belgium, Spain are 2.98, 1.37, 1.03, 0.546 in ten thousand respectively (4). No data are available for Iran in the report of CF by WHO (3). However there are a few papers reporting different statistics of CF in different regions of Iran. For instance, while no confirmed case of CF has been reported in southern Iran (5), there is a report from north-west of Iran on CF prevalence of 7.98 in 100 thousand during the 5-year period (2004-2008)(6) in addition to a study reported growth pattern and nutritional intake of 34 infants with CF in East Azerbaijan province (7). Moreover, spectrum of CFTR gene mutations in 200 Iranian Azeri Turkish Patients with Cystic Fibrosis has been examined and reported in another study (8).

Registries are considered essential tools designed to measure all health-related aspects of cystic fibrosis (CF) and to compare clinical data from different centers and countries. Over the last 25 years, several national registries of CF have been set up (9). European Committee of Experts on Rare Diseases emphasizes the importance of the registry system on rare diseases such as CF. This is due to the fact that the registry system can be very useful in cases of rare disease such as cystic fibrosis in providing an integrated resource for improving patient care and research on the disease (10, 11).

Minimum Data Set is a common set of data items that should be used to collect and report data in the registry (12). To best of our knowledge, no research has been undertaken so far in order to identify minimum data set for cystic fibrosis in Iran. This paper represents our attempt to identify minimum data set for cystic fibrosis registry system in Northwest of Iran.

2. METHODS

To determine the minimum data set required for establishing registry system of cystic fibrosis, the systems of selected countries including Netherlands (13), the US (14), Ireland (15), UK (16), France (17, 18), Australia (19), Brazil (20), Canada (21), Belgium (22) and New Zealand (23) as well as the registry system of European Cystic Fibrosis Society (24) were studied.

Considering the commonalities and differences observed among data elements of the studied registry systems and regional demands, an initial set of data elements was proposed by the researchers. Then a group of multidisciplinary experts consisted of epidemiologists, pediatricians, and CF specialists were asked to review and score the initial set based on their importance by using a nine-point Likert scale ranging from 1 to 9 where 1 referred to concept of "no important for inclusion in MDS" and 9 indicated the statement of "highly important for inclusion in MDS". Data elements that were scored as important or highly important by more than 50 percent of the experts were included in the final minimum data set.

In next stage of the research, availability of data on the agreed minimum data set was evaluated through reviewing the medical records of 144 patients (191 episode of care) hospitalized with diagnosis of cystic fibrosis in Tabriz children hospital from 2009 to 2014.

3. RESULTS

3.1. Identification of initial data elements

Overall six classes of data (including 46 data items) were identified in the selected cystic fibrosis registry systems: patient demographics, administrative data, survival status, diagnostic procedures, genetic and clinical manifestations, and therapeutics. Overall 34 data elements were determined as an initial set as follows:

- Patient demographics: name, gender, age, weight, height, BMI, date of birth, age at diagnosis, job, place of birth, socioeconomic status, and time off from work or school
- Administrative data: CF centre identification code, patient identification code, year of follow-up, cost of hospitalization, frequency of hospitalization per year, and date of encounter
- Survival data: death date(if any), and cause of death
- Diagnostic procedures: sweat test, genetic test, antenatal screening, exercise tolerance test, and glucose tolerance test
- Disease genotype and clinical manifestation: CF genotype, signs and symptoms, FEV1, FVC, and complications
- Therapeutics: medications, and organ transplantation

3.2. Agreed minimum data set

Data elements scored as highly important or important at least by more than 50 percent of the experts are presented in table 1.

More than 75%	51-75 %	51-75 %
Date of birth	Name	Date of encounter
Age at diagnosis	Gender	Organ transplantation
Cause of death	Age	Time off from work or school
CF complications	Weight	Follow-up year
FEV1	Height	Glucose tolerance test
FVC	BMI	Exercise tolerance test
Frequency of hospitalization per year	Patient identification code	Medications
Sweat test	CF centre identification code	Antenatal screening
Signs and symptoms	Socio-economic status	Cost of hospitalizations
	Birth Place	Genetic test
	Death date	Genotype

Table 1. *Minimum data set approved by the experts for CF registry*

3.3. Availability of the data

As figure 1 depicts availability of data in administrative category and survival class is 100 percent. Collecting data on medications was feasible in 100% of the cases as well. In class of demographic data, availability of patient name, age, gender, place of birth, and date of birth was 100 percent. In group of diagnostic procedures, partial availability of data was observed for sweat and genetic test. However no data were found on antenatal screening, exercise tolerance test, and glucose tolerance test.

4. DISCUSSION

This paper represents the first attempt undertaken to develop minimum data set for registry system of cystic fibrosis in Northwest of Iran. Comparative study of the registry systems provided a foundation for defining the initial MDS. There were six different classes of data elements including patient

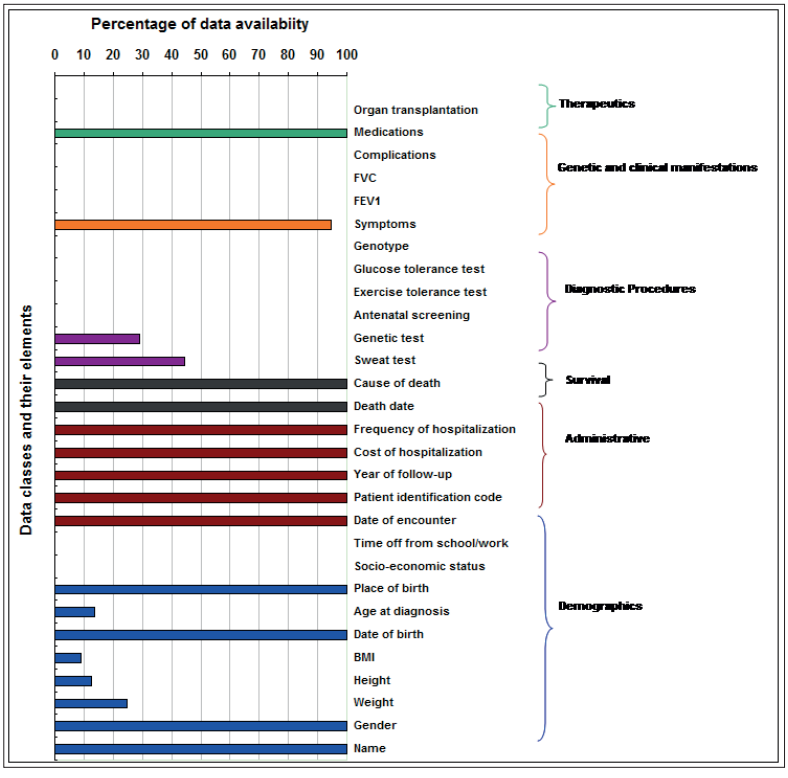

Figure 1. *Percentage of the data availability for CF registry in patient records*

demographics, administrative data, survival data, diagnostic procedures, genetic and clinical manifestation, and therapeutics. Majority of data elements from all six classes were evaluated as highly important or important by the experts. This is similar to the classes of data determined as minimum data set for athlete health records (25), physiotherapy (26), breast cancer (27), orthopedic injuries in Iran (28), nursing (29) by their related experts. This is also in line with information classes found in data content residing in GP systems (30). This can reflect the importance of these categories in different domains of health care system. This can be also due to the fact that minimum data set can be used in variety of use cases: for patient care in individual level; for assessment of system and care provider in organizational level; and for national and international comparisons in aggregated level (12). Moreover minimum data set can contribute to realization of conceptual interoperability throughout all these levels (31).

Reviewing medical records of patients with CF revealed availability of the data in real world. Majority of data in administrative and demographic categories were highly available in the patient records. This is viable as the data items such as patient identification code, patient name and encounter date are important for linking records from multiple resources (32) or data items such as age, gender,or birth place can be used for standard sociodemographic comparisons or reports as they are among high priority data items determined by CF data network (33). However it should be noted that patient identification code used in the medical records could only identify patient in the hospital not throughout the entire health system. Therefore the unique patient identification number with capability of recognizing patient across the entire health system is the missing element.

High priority given by the experts on date and cause of death and their full availability are in consistent with legal enforcement for recording such data (34). Medication data were found to be available in 100 percent of the cases. This is not surprising as these data are at the core of the direct patient care.

Partial availability of data for sweat test and genetic test was observed. Although sweat test is done for diagnosing all cases, and genetic test is carried on for most of the patients, but in most cases it is conducted in outpatient services and clinics that are not connected with the inpatient services and their results are usually kept by patient's family. This may also be attributed to lack of linkage or integration among different information silos across CF care related centers, including the laboratories or clinics. This may also reflect lack of appropriate data flow. Use of unique patient identifier across the whole continuum of health system can facilitate data flow and integration of patient care.

Despite high priority given to data items on diagnostic tests such as antenatal screening, exercise tolerance test and glucose tolerance test, no data was found on them in the hospital patient records. It should be noted that the problem with glucose tolerance occurs after age of 10 while all cases in this study are neonates and infants when they are diagnosed or admitted to the hospital. Exercise tolerance test is not a routine test and in case it is done, its data is not entered into hospital records as it is undertaken in private clinics. Antenatal screening is not also done because there is no precise statistic of patients with CF in Iran. Unavailability of data on FEV1 and FVC is due to the fact that respiratory tests are not taken place in hospital but in private ambulatory services and clinics.

Lack of data on organ transplant is not surprising as the lung transplant for patients with CF has just newly introduced in Iran.

Finding about data availability in this research was restricted to children hospital records. Other resources in genetic laboratory centers, or clinics, or other related centers and hospitals were not studied. Lack of unique patient identifier across the entire health system seems to be the most important limit in integrating the related information resources. In addition lack of coding practice for ambulatory and outpatient health services makes it unfeasible to locate and retrieve data residing in the related centers.

5. CONCLUSION

This study presents minimum data set required for establishing cystic fibrosis registry in Northwest of Iran. Minimum data set can be also useful in designing electronic patient records or registry for those suffering from CF toward integration of their fragmented records across continuum of the health care system and for the shared patient care.

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CONFLICT OF INTEREST: NONE DECLARED.

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Preconception/Prenatal Family Health History Questionnaire

Today's date: _____ Person completing questionnaire: _____

	Patient	Partner/spouse
Name		
Date of birth		
Occupation		
Marital status (married, divorced, widowed, single)		
Last grade completed		
Height		
Weight		
Adopted	◯ Yes ◯ No	◯ Yes ◯ No

Past medical history (check all that apply)

	You	Partner	Explain checked items, include year or age
Surgeries	◯	◯	_____
Hospitalizations	◯	◯	_____
Major illnesses	◯	◯	_____
Chronic medical problems	◯	◯	_____
Allergies	◯	◯	_____
Learning problems	◯	◯	_____
Behavior problems	◯	◯	_____
Mental illness	◯	◯	_____

Ethnic Background

Where did your and your partner's ancestors come from before the United States? (check all that apply)

	You	Partner
Mediterranean (e.g., Italian, Greek)	◯	◯
European Caucasian (e.g., Irish, English, German)	◯	◯
African or African-American	◯	◯
Ashkenazi Jewish	◯	◯
Hispanic (e.g., Puerto Rican, Dominican, Mexican)	◯	◯
Cajun or French Canadian	◯	◯
Southeast Asian (e.g., Laotian, Chinese, Vietnamese)	◯	◯
Indian (from India)	◯	◯
Middle Eastern (e.g., Lebanese, Iranian, Egyptian)	◯	◯
Native American	◯	◯
Other _____	◯	◯

Preconception/Prenatal Family Health History Questionnaire

march of dimes

Date of first day of last menstrual period _____
Your age _____ If pregnant: your age at delivery _____ Current age of partner _____

Do you:
(if pregnant, also include all exposures since last menstrual period)

	Yes	No
Take any medications (prescription or non-prescription)?	◯	◯
Take a daily multivitamin or folic acid supplement?	◯	◯
Drink alcohol (beer, wine, hard liquor)?	◯	◯
Smoke cigarettes?	◯	◯
Use any recreational drugs (cocaine, marijuana, heroin)?	◯	◯

For any "**yes**" answers, describe below, including amounts and dates, if known.

_____

_____

Have you had:	**Yes**	**No**	**Have you been exposed to:**	**Yes**	**No**
Chicken pox (varicella)	◯	◯	Radiation (X-rays)	◯	◯
Fifth disease (parvovirus)	◯	◯	Chemicals (e.g., organic solvents, mercury)	◯	◯
Cytomegalovirus	◯	◯			
Toxoplasmosis	◯	◯	Raw meat (e.g., eaten steak tartar)	◯	◯

For any "**yes**" answers, describe below, including dates and details, if known.

_____

_____

_____

Did your mother take a medication called
"DES" while pregnant with you? ◯ **Yes** ◯ **No** ◯ **I do not know**
Were you born preterm? ◯ **Yes** ◯ **No** ◯ **I do not know** If so, how early? _____weeks

Do you have a personal history of:	**Yes**	**No**
Thyroid disease	◯	◯
Diabetes	◯	◯
Seizures	◯	◯
Hyperphe or phenylketonuria (PKU)	◯	◯
Deep vein thrombosis	◯	◯
Lupus	◯	◯
Other chronic conditions:	◯	◯

_____

Please list total number of prior:

Pregnancies	_____
Full-term births	_____
Multiple gestation pregnancies (e.g., twins)	_____
Preterm births (<37 wks)	_____
Preterm labor (<37 wks)	_____
Stillbirths	_____
Miscarriages (<24 wks)	_____
Elective abortions	_____
Living children	_____

Preconception/Prenatal Family Health History Questionnaire

For the questions below, please check the boxes for those conditions that have occurred in your or your partner's/ spouse's families. Include yourself AND your spouse/partner, as well as your and his siblings (full and half), parents, children, grandparents, aunts, uncles, nieces, nephews and first cousins, if possible.

	Your Family	**Partner's Family**	**Who is affected?** (you, parent, sib, etc.)
Anencephaly or spina bifida (openings in the skull or spine)	◯	◯	_____
Hydrocephalus (water on the brain)	◯	◯	_____
A large, small or unusually shaped head	◯	◯	_____
Blindness or other vision problems	◯	◯	_____
Cataracts	◯	◯	_____
Glaucoma	◯	◯	_____
Deafness or significant hearing loss	◯	◯	_____
Unusual shape, size or position of ears	◯	◯	_____
Cleft lip and/or cleft palate (opening in lip and/or roof of the mouth)	◯	◯	_____
Dental problems (missing, extra or abnormally formed teeth)	◯	◯	_____
Speech problems	◯	◯	_____
Congenital heart defect (e.g., "hole" in the heart)	◯	◯	_____
Heart attack or coronary artery disease	◯	◯	_____
Respiratory disease or chronic lung condition	◯	◯	_____
Asthma	◯	◯	_____
Allergies	◯	◯	_____
Cystic fibrosis	◯	◯	_____
Alpha-1-antitrypsin deficiency	◯	◯	_____
Pyloric stenosis	◯	◯	_____
Birth defects of the bowels or intestines	◯	◯	_____
Kidney problems	◯	◯	_____
Polycystic kidneys, missing or extra kidneys	◯	◯	_____
Genital or urinary tract defects	◯	◯	_____
Congenital hip dislocation (born with dislocated hips)	◯	◯	_____
A birth defect of an arm or a leg	◯	◯	_____
Unusually formed bones or many broken bones	◯	◯	_____
Scoliosis (curved spine)	◯	◯	_____

Preconception/Prenatal Family Health History Questionnaire

	Your Family	Partner's Family	Who is affected? (you, parent, sib, etc.)
Unusually formed hands or feet (including club foot)	◯	◯	
Very short or tall stature	◯	◯	
Dwarfism	◯	◯	
Marfan syndrome	◯	◯	
Muscle weakness or poor coordination	◯	◯	
Muscular dystrophy	◯	◯	
Mental retardation or developmental delay	◯	◯	
Learning disabilities or a slow learner	◯	◯	
Attention deficit or hyperactivity	◯	◯	
Autism	◯	◯	
Seizures, epilepsy or convulsions	◯	◯	
Down syndrome or other chromosome syndrome	◯	◯	
Fragile X syndrome	◯	◯	
Tay-Sachs disease	◯	◯	
Canavan disease	◯	◯	
Phenylketonuria (PKU)	◯	◯	
Gaucher disease	◯	◯	
Alzheimer's disease or other form of dementia	◯	◯	
Huntington's disease	◯	◯	
Neurofibromatosis	◯	◯	
Schizophrenia or other mental illness	◯	◯	
Manic depression (bipolar)	◯	◯	
Unipolar disorder (severe depression)	◯	◯	
Birthmarks or unusual growths on skin	◯	◯	
A chronic skin condition (e.g., eczema)	◯	◯	
Patches of different colored hair	◯	◯	
Patches of different colored skin	◯	◯	
Bleeding or clotting disorder (e.g., hemophilia)	◯	◯	
Hereditary anemia (e.g., thalassemia, sickle cell, other)	◯	◯	
Deep vein thrombosis	◯	◯	
Factor V Leiden	◯	◯	
High cholesterol	◯	◯	
Stroke	◯	◯	
Hemochromatosis (iron storage condition)	◯	◯	

Preconception/Prenatal Family Health History Questionnaire

	Your Family	Partner's Family	Who is affected? (you, parent, sib, etc.)
Diabetes	◯	◯	_____
Thyroid disease	◯	◯	_____
High blood pressure or hypertension	◯	◯	_____
Breast cancer	◯	◯	_____
Ovarian cancer	◯	◯	_____
Colon cancer	◯	◯	_____
Other cancers or tumors	◯	◯	_____
Born preterm (<37 weeks)	◯	◯	_____
Stillbirths	◯	◯	_____
Infant or childhood deaths	◯	◯	_____
Two or more miscarriages or pregnancy losses (in the same person)	◯	◯	_____
Infertility or sterility (unable to get pregnant or have children)	◯	◯	_____
Premature ovarian failure (early menopause)	◯	◯	_____
Primary amenorrhea (never had a period)	◯	◯	_____

Have you, your partner/spouse, or anyone in your family had genetic testing? ◯ **Yes** ◯ **No**
If yes, please explain:

_____

_____

Are you and your partner/spouse related as first cousins or in any other way as blood relatives? ◯ **Yes** ◯ **No**
If yes, please explain:

_____

_____

For office use only

Significant findings:

Recommendations:

Date discussed with patient/family _____HCP name/initials _____

Patient/parent/guardian signature X_____

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Elevated titanium levels in Iraqi children with neurodevelopmental disorders echo findings in occupation soldiers

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Abstract Anthropogenic release of pollutants into the environment is especially harmful to growing fetuses and young children. These populations are at an increased risk of damage because exposure to pollutants during critical periods of development can cause many impairments. Children's exposure to mixtures of metals could be responsible for the rising numbers of neurological disorders surfacing in Iraqi children. Titanium (Ti) and magnesium (Mg) are heavily used in war industries. Exposure to Ti and Mg has been linked to the dust in occupation soldiers' lungs. Hair samples of children in Hawija, Iraq (n=13) contained significantly higher levels of Ti compared to Iranian children (n=13) living near the Iraqi border (2080±940 vs 707±421 μg/kg, p<0.0001). Magnesium was 1.7 times higher in Hawija children compared to Iranian children (115,763±118,155 vs 67,650±46,729 μg/kg). In samples from Hawija, Ti was 1.3 times higher in children with neurodevelopmental disorders (2198±1108 vs 1942±779 μg/kg), and Mg was 1.9 times higher in children without neurodevelopmental disorders (155,618±140,791 vs 81,602±91,940 μg/kg). Lead, arsenic, and cadmium in Hawija children with neurodevelopmental disorders (n=6) were 2.5, 2.2, and 1.37 times higher compared to non-disabled children (n=7). To get a clear understanding of the current status of neurodevelopmental disorders in Iraqi children and to determine the magnitude of this suspected global health issue, registries should be set up to compile and aggregate data from hospitals, clinics, and health centers across the country. Functional registries can develop collaborations with researchers toward finding causes of these disorders in Iraqi children and toward preventing them.

Keywords War pollution · Neurodevelopmental disorders · Hawija · Fallujah · Titanium · Magnesium

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Introduction

Global public health is harmed by the anthropogenic release of pollutants into the environment. Mining, waste incineration, hazardous waste sites, and war have been shown to release harmful toxicants into otherwise

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healthy environments, putting populations residing nearby at risk for adverse health impacts (Shields et al. 1992; Liao et al. 2010; Cordier et al. 2004; Wright et al. 2006; Al-Sabbak et al. 2012). The most vulnerable populations (i.e., elderly, pregnant mothers, growing fetuses, and young children) are most severely affected by the environmental release of toxicants.

It is now widely accepted that environmental pollutants, including metals, can disrupt neurodevelopmental processes during critical periods of development, resulting in effects on sensory, motor, and cognitive function. We now know that developmental exposure to chemicals can have adverse effects on the structure and/or function of the nervous system and can harm neurodevelopmental processes (Schardein and Keller 1989; Jurewicz et al. 2013). Among metals, lead and mercury are recognized causes of neurodevelopmental disorders as well as subclinical brain dysfunction. Prenatal exposures to these metals during in utero development can cause brain damage in the developing fetus. Fetal brain damage can result from metal exposure levels which are much lower than those affecting the adult brain and its normal function. Increasing evidence suggests that chemicals can also be the cause of neurodevelopmental damage in the unborn.

The small city of Hawija is located approximately 175 km north of the capital, Baghdad. In 2004, a school was taken over and converted into an American military base, Operating Base McHenry. Overall, a total of 200 military camps, 141 forward operating bases, and 69 combat outposts have operated in Iraq since the 2003 invasion. Multiple waste types, generated by these military installations, have been disposed of in massive open-air burn-pits across Iraq (Kennedy 2008; Jacobs 2013; Woodall et al. 2012). Another major concern in Iraq has been exposure to uranium. A 2007 publication of the United Nations Environment Program (UNEP) estimated that 1000 to 2000 metric tons of depleted uranium were fired during the 2003 war in Iraq.

It has been reported that, under the Logistics Civilian Augmentation Program (LOGCAP), open-air burn-pits, as wide as 10 acres, continuously burned waste on US military bases throughout Iraq until 2010. After considerable health complaints from the US military personnel, the US Congress voted to prohibit the burn-pits, with an amendment to the National Defense Authorization Act. Subsequently, federal law required the establishment of a registry for eligible individuals who may have been exposed to toxic airborne chemicals and fumes caused by those open burn-pits (Kime 2013; Hansia 2014). Jet fuel was commonly utilized to burn and dispose of plastics, batteries, appliances, medicine, dead animals, and even human body parts in these open burn-pits. A recent report has suggested that styrofoam (i.e., styrene), electronics, rubber tires, explosives, and asbestos insulations have also been disposed of in these open-air burn-pits (Kennedy 2008).

Styrene is a known neurotoxicant. In humans, chronic exposure to styrene has been linked to effects on the central nervous system. In addition, an increased frequency of spontaneous abortions and a decreased frequency of births have been reported in a study on the reproductive effects of styrene in humans (ATSDR, Toxicological Profile for Styrene; HSDB, online database). Cadmium, copper, and lead are created in abundance when burning electronic waste and plastics (Brigden et al. 2005; Nnorom and Osibanjo 2009). Similarly, because toxic heavy metals are an integral part of rubber, explosives, and batteries, emanations laden with heavy metals can result from burning them (Ahamd et al. 2009; Bushuyev et al. 2012; Cameron et al. 2011). Increasingly, emissions from the burning of such compounds have been scrutinized as a significant global source of harmful pollutants.

During the past decade, hundreds of American soldiers, who temporarily lived on various US military bases in Iraq and Afghanistan where open burn-pits were heavily used to dispose of waste, have reported medical problems as a result of exposure to those burn-pits. A few studies have examined this problem (Conlin et al. 2012; Smith et al. 2012; King et al. 2011). Additionally, recent investigations have linked titanium (Ti) and magnesium (Mg) to the dust found in Iraq and Afghanistan veterans' lungs (Szema et al. 2014). Both metals are heavily used in the war industry and in the manufacture of weaponry. While soldiers' exposure to toxic compounds is transient and will discontinue after they leave the polluted environment, the local populations' exposure to toxic pollutants remains uninterrupted. We therefore expect Hawija residents to be chronically exposed to a persistent cocktail of toxic metals.

Parallel with this environmental condition, doctors and health professionals in Hawija have been witnessing increasing numbers of children with neurological disorders. Increases in birth defects and adverse reproductive outcomes have been linked to public contamination with lead and mercury in two other Iraqi cities, Fallujah and

Basra, where numerous US military installations have also been operating since 2003.

In this setting, we hypothesized that the hair metal content of Hawija children with neurodevelopmental disorders would be higher than that of non-disabled children living in the same town. We also expected to see a continuum of decreasing severity of neurodevelopmental disorders (Hawija < Fallujah and Basra) as we move away from areas with large aggregates of military bases and with a history of heavy urban military bombardments.

Materials and methods

Study area

Hawija is a city of 40,000 people located 175 km north of Baghdad (Fig. 1). The latitude (34.00371) and the longitude of Hawija (44.39538) have been reported using a global positioning system (GPS). The prevailing climate in Hawija is known as a local steppe climate. Throughout the year, there is little rainfall. The Köppen-Geiger climate classification considers Hawija a hot semi-arid climate, with generally rainless summers and wetter winters. Temperatures in Hawija often reach 56 °C in the long and dry summer. A National Environmental Strategy for Iraq publication which was released in 2012 suggests that desertification has had a negative impact on the environment and has directly affected the life of the population by increasing the rates and frequencies of sand and dust storms in our study area to unprecedented levels.

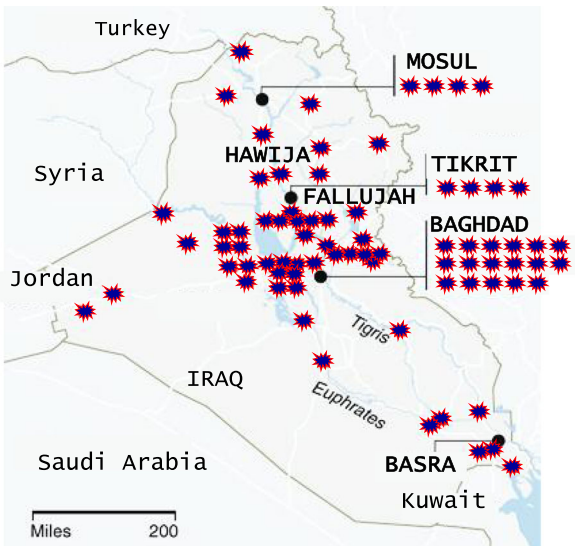

Fig. 1 Map of major US military installations in Iraq since 2003. Hawija is approximately 175 km north of the Capital, Baghdad

Questionnaires, participant consent, and sample collection

In September 2013, local health workers and medical staff in Hawija sought participants for a metal biomonitoring study of the city. Health workers recruited seven mothers and two of their children into this study. Each mother enrolled two siblings into the study, one non-disabled child (n=6) and another child with a disability (n=7). Using a 48-item questionnaire, mothers were interviewed and signed a consent form permitting the team to use all information for research purposes only. Mothers also consented to the collection of hair samples from their children for metal analysis. Utilized questionnaire examined the reproductive history of the mother, residence history for the family, health and disease during pregnancy, drug use during pregnancy, smoking and alcohol use, source of water for the family, and exposure to potential war contaminants. Simultaneously, a uranium exposure and contamination self-assessment questionnaire with checklists was also completed by each participating mother (Table 1). This tool was designed to determine the movement of the individual into and out of polluted environments, the duration of such events, and potential physical manifestations of exposures (i.e., nose bleeds, skin irritation or stinging sensations, coughs, etc.). At the same time, children's hair (approximately 0.5 g) was collected, with scissors, from the nape of the head and placed in clean paper envelopes, then sealed and transported to the laboratory.

Hair samples' treatment, digestion, and ICP-MS analysis

The certified reference materials (NCS DC 93347 and NCS ZC 81002) were purchased from Brammer Standard Company, Inc. (Benfer Rd Houston, TX) and prepared using two different methods. One was closed microwave digestion, and another was hot block digestion. Hot block digestion was performed at a lower temperature to avoid Hg loss. Data generated from hot block and microwave digestion procedures were consistent between the two digestion methods, indicating the appropriateness of either procedure for sample digestions. Once samples were digested, digests were

Table 1 Results of uranium exposure or contamination self-assessment questionnaire, responses of Hawija mothers who participated in the current study in September 2013

Uranium exposure and contamination self-assessment questionnaire							
	Mother's responses						
	8b	3b	10a	1b	5b	2a	6a
Was your residence ever bombed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were you in your house when it was bombed?	Yes	Yes	Yes	No	No	Yes	Yes
Do you live near a military installation?	Yes	No	No	Yes	No	No	Yes
During bombings did you experience any of the following?							
Nose bleed or runny nose	Yes	Yes	No	No	No	No	No
Throat, nose, or mouth irritation or stinging	Yes	Yes	Yes	No	No	Yes	Yes
Skin or eye irritation or burning	Yes	Yes	Yes	Yes	Yes	No	Yes
Dry coughs	Yes	Yes	Yes	No	Yes	Yes	Yes
Cold and flu like symptoms	Yes	Yes	Yes	Yes	Yes	Yes	Yes
After bombings did you experience any of the following?							
Unusual tiredness, fatigue, weakness	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intermittent fevers	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sweeting at night	Yes	Yes	No	No	Yes	Yes	Yes
Short-term memory loss	No	Yes	Yes	Yes	Yes	Yes	Yes
Disorientation or confusion	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Depression or loss of initiative	No	No	Yes	No	Yes	Yes	Yes
Headaches	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Recurring or continuous pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chronic cold or flu	Yes	Yes	Yes	No	No	Yes	Yes
Asthma, chronic bronchitis	Yes	No	No	No	No	Yes	Yes
Stinging sensation when urinating	No	Yes	Yes	Yes	Yes	Yes	Yes
Gastrointestinal problems	No	No	Yes	Yes	Yes	Yes	Yes

analyzed for multiple elements on the Agilent 7700x inductively coupled plasma-mass spectroscopy (ICP-MS). The limit of detection for the method is expressed as the mean blank signal +3× standard deviation of the blanks (at least 6 replicates) for each of the elements in micrograms per kilogram: Al < 1000; Mg < 600; Ti < 50; Cu < 90; As < 60; Cr < 40; Se < 30; V, Mn, and Pb < 20; Hg and Th < 10; Zn < 5; Cd < 4; Ni < 3; Fe, Co < 2; Mo, U < 1.

All hair samples were hot block digested for analysis

For hot block digestion, hair was placed in clean polypropylene tubes, rinsed with deionized (DI) water once, and then rinsed with 5 ml of methanol. Samples were then washed twice with DI water and dried in an incubator for 8 h at 50 °C. Accurately weighed 0.05 g of hair, along with NCS ZC 81002 Standard Reference Material for hair, was put in a clean tube and 0.5 ml of concentrated HNO_3, and 0.5 ml of H2O2 was added. Samples were then heated in a hot water bath for 1 h at 80 °C, and then allowed to cool. Of DI water, 9 ml was added, and tubes containing samples were then capped and shaken well before ICP-MS analysis.

For microwave digestion, samples were similarly washed and dried. Then, 0.1 g of clean and dried hair and standards were placed in a clean microwave vessel, and 2 ml of concentrated HNO_3 and 2 ml H2O2 were added. The reaction was allowed to subside after approximately 30 min to 1 h; then, vessels were placed in a microwave for 40 min for digestion at 50 % of full power wattage. Microwaved samples were removed

from the microwave and allowed to cool to room temperature. Digested samples were then transferred into clean tubes, and 6 ml of DI water was added. Samples were capped and shaken before ICP-MS analysis.

Statistical analysis

An IBM SPSS software (version 21) was used for all analysis. A one-way analysis of variance was followed by post hoc Bonferroni multiple comparisons test to determine the source of significance. Significance level was set at $p<0.05$.

Results and discussion

The average age of the participating mothers ($n=7$) was 30±4.75 (range 22 to 34). Children with developmental disability ($n=7$) were on the average 4.14±2 years old (range 6 to 1). Non-disabled children ($n=6$) were 5± 4.32 years old (range 12 to 1). Gestational age for children with developmental disability and non-disabled children were 36.67±0.8 and 37±0.7 weeks, respectively. Mothers did not smoke or drink during pregnancy, and only one mother took painkillers according to the doctor's prescription. No one had taken antidepressants during pregnancy. A total of six miscarriages and four stillbirths were reported by the mothers. Two miscarriages had occurred in 1992 and one in 1998. The remaining miscarriages had occurred after 2003. Children with neurodevelopmental problems in this study were diagnosed by licensed local physicians suffering from brain damage, epilepsy, continuous body seizures, missing fingers and toes, or disfigured limbs (Fig. 2.)

Table 2 reports metal levels (mean±STDEV in μg/kg) measured by ICP-MS. We found that the levels of toxic metals, including lead (Pb), arsenic (As), and cadmium (Cd) in children with neurodevelopmental disorders ($n=6$), were 2.5, 2.2, and 1.37 times higher compared to that of non-disabled children ($n=7$). Mercury hair content was 792±1207 μg/kg in the non-disabled children and 698±1190 μg/kg in the disabled children. Reported differences were not statistically significant ($p>0.05$). Children's uranium exposure appeared to be low in both non-disabled and disabled Hawija children.

Mothers' responses to the uranium exposure and contamination self-assessment questionnaire are provided in Table 1. All of the participants' homes had been bombed at least once, and four of their neighbors' houses had also been bombed. Three of the residences of participants had been the target of white phosphorous attacks. Three out of the seven mothers said they lived near the military base in town. Cold and flu-like symptoms; unusual tiredness, fatigue, or weakness; intermittent fevers; disorientation or confusion; headaches; and recurring or continuous pain (in legs and back) were most frequently recalled by the mothers during and after bombardment. Nose bleed or runny nose, and asthma and chronic bronchitis were least reported. Half of the participants reported depression or loss of initiative following bombardment. Our data suggests that participants had been exposed to varying degrees of pollution created by bombing or by air pollution as a result of living near a military base with open burn-pits. Children's uranium exposure appeared to be low in both non-disabled and disabled Hawija children (Table 2).

Previous reports of hair metal content in children with birth defects from Fallujah, Iraq (Al-Sabbak et al. 2012; Alaani et al. 2011) show 3.7 times higher lead than that of the levels we report in Hawija children with neurodevelopmental disorders. Mercury was 12-fold higher in Fallujah children with birth defects compared to Hawija children with neurodevelopmental disorders. Limited numbers of observations in some groups, combined with high variability in metal levels within groups, make data interpretation difficult. However, a trend is detectible (Figs. 3 and 4). In Iraqi children, born with neurological disorders, the severity of neurodevelopmental effects is more pronounced as lead levels increase. The city of Fallujah is surrounded by military bases and has been the target of more bombings compared to that of Hawija, where bombings have been less frequent and the numbers of military bases are also fewer (Fig. 1). It can therefore be argued that children of Fallujah—who have a higher likelihood of exposure to war-related pollutants—exhibit more severe neurodevelopmental conditions than that of children of Hawija.

Titanium and magnesium are elements of the war industry

Titanium and Mg are integral to the war industry, and both elements are key to the manufacture of weaponry. Titanium has been widely used in the US military since

Fig. 2 Photo of the participating children: *a* and *b* brain disorder and disfigured limbs; *c*, *d*, and *e* epileptic with general body seizures

Table 2 List of metals in children's hair from Hawija, and previously reported values from Fallujah analyzed by ICP-MS

Hair metal	Mean±STDEV (range) µg/kg Hawija children		Mean±STDEV µg/kg Fallujah children	
	Normal (n=6)	With neurodevelopmental disorder (n=7)	Normal (n=11)	With birth defects (n=31)
Cr	436.3±417 (91–1158)	282.7±64.2 (184–343)	748±412	393±335
As*	83 (>20–83)	180±94 (112–319)	148±70	145±111
Cd*	83±68 (7–164)	114±77 (16–208)	72±69	221±786
Hg	792±1207 (43–3191)	698±1190 (39–3250)	1414±3854	8282±25,844
Pb*	3714±2216 (1149–4976)	9181±9752 (370–26,245)	11,277±27,781	34,022±128,815
Mn*	2415±1718 (304–5125)	2915±2761 (250–4049)		
Al*	29,883±18,377 (13,531–57,022)	30,475±16,973 (10,004–56,846)		
V*	275±75 (<20–356)	422±214 (<20–624)		
Fe*	31,566±17,345 (12,684–56,776)	35,545±17,053 (16,639–65,808)		
Co*	49±27 (9–83)	69±60 (180–12)	301±210	89±53
Ni*	400±220 (108–687)	427±262 (126–925)		
Cu	43,732±76,504 (5634–199,722)	13,803±6134 (8213–23,463)		
Zi*	173,738±86,459 (94,975–321,590)	183,400±94,622 (85,445–363,804)		
Se	601±55 (518–676)	512±189 (202–734)		
Mo*	56±28 (19–94)	72±53 (29–180)		
U*	16±17 (3–50)	19±13 (4–46)	61±41	36±41

Values are mean±standard deviation

Asterisk larger numerical values in Hawija children with neurodevelopmental disorders compared to normal children from the same city, but no statistical differences (p>0.05)

Fig. 3 Selected photos of children born in Fallujah between 2008 and 2010, showing severe neurodevelopmental disorders, in the form of multiple birth defects

the 1960s. It is favored because it weighs less than other metals and it does not rust. It is estimated that about 55 % of the Ti manufactured in North America is utilized in the military and aerospace industries. Titanium is used extensively in US weapons systems, machine guns, ground vehicles, combat vehicles, weapons platforms, tanks, armored personnel carriers, pressure vessels in ballistic missiles, and in Blackhawk and McDonnell Douglas Apache helicopters (Titanium Structures for Army Systems, SM2 KN4-1).

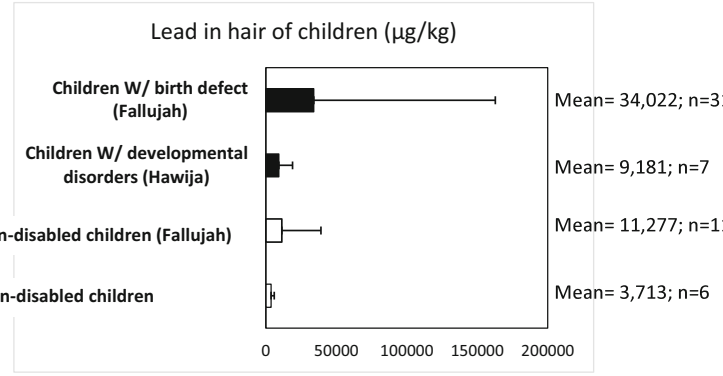

Fig. 4 A comparison of lead in children's hair samples from Hawija and Fallujah (µg/kg)

Similarly, Mg has ballistic and structural applications in the military, and its use has been growing since the Second World War. Magnesium is widely used in the making of tanks, artillery, armored vehicles, and other military equipment. Magnesium is utilized by the military as a major incendiary agent. It has been used in cluster bombs for its capacity to burn persistently for an appreciable length of time with a very high temperature and cannot be easily extinguished (Jones et al. 2012).

Exposure to Ti and Mg has been linked to dust found in the lung tissue of US occupation soldiers (Szema et al. 2014). Hair samples of Hawija children ($n=13$) contained three times more Ti (2080±940 μg/kg) than that of hair samples of Iranian children ($n=13$) who live in Khoram Shahr near the Iraqi border (707±421 μg/kg; unpublished forthcoming data, $p<0.0001$). Magnesium was 1.7 times higher in Hawija children than in Iranian children (115,763±118,155 vs 67,650±46,729 μg/kg). Ti levels are rarely reported in children's hair; however, Table 3 contains a current review of the literature on Ti and Mg levels in children's hair. Titanium in hair samples from Hawija have the highest levels of this metal ever reported in children's hair globally.

In samples from Hawija, Ti was 1.3 times higher in children with neurodevelopmental disorders (2198±1108 μg/kg) than that in children without neurodevelopmental disorders (1942±779 μg/kg). Mg was 1.9 times higher in children without neurodevelopmental disorders (155,618±140,791 μg/kg) than that in those with the disorder (81,602±91,940 μg/kg). Interestingly, Mg has been shown to protect against brain damage by diminishing neuronal apoptosis (Turkyilmaz et al. 2002). Moreover, a review of the literature has found associations between Mg treatment and significantly reduced risk of infant mortality and cerebral palsy (a neurodevelopmental disorder of major concern). Antenatal treatment with Mg during premature deliveries has been suggested to have health benefits for the infant (Wolf et al. 2012). Our findings corroborate with the available literature on the beneficial and protective effects of Mg on brain development. Hawija children with higher Mg levels appear to have been protected against neurodevelopmental damage.

In Iraq, an estimated 1000 to 2000 metric tons of depleted uranium was fired during the 2003 US invasion of that country (UNEP 2007, Annual Report). The explosion of depleted uranium bombs can develop temperatures that exceed 3000 °C (annual report, 1978). The magnitude of this combustion can vaporize everything found on battlegrounds, including Ti and Mg containing material. As the vaporized materials cool, nanoparticles are created and are scattered in the environment. Inhalation or ingestion of these mainly metallic particles can cause pathologies in humans (Gatti and Handbook 2005; Nemmar et al. 2002).

Recent laboratory studies have linked in utero titanium nanoparticle exposures to brain cell necrosis, hippocampal cell apoptosis, and neurotoxic effects in offspring (Ze et al. 2014; Mohammadipour et al. 2014), implying potential for brain damage in the exposed offspring. It has been suggested that the interaction of titanium dioxide nanoparticles with other chemicals

Table 3 A review of literature on Ti and Mg levels in children's hair

Reference	Year	Country	*N* Children	Instrument	Titanium (μg/kg)	Iron (μg/kg)	Magnesium (μg/kg)
Blaurock-Busch et al.	2011	Egypt	25	ICP-MS	560	11,000	70,000
Peña-Fernández et al.	2014	Spain	117	ICP-AES	900	–	–
Raposo et al.	2014	Spain	112	ICP-MS	1300	17,400	61,000
Senofonte et al.	2000	Italy	396	ICP-AES	790	19,000	28,000
Forthcoming, unpublished		Khoram Shahr, Iran	13	ICP-MS	707	22,969	67,650
This study	Present	Hawija, Iraq	13	ICP-MS	2080*	33,708	115,763
Park et al.	2007	Korea	655	ICP-MS	–	12,290	12,620
Al-Farsi et al.	2013	Oman	27	ICP-MS	–	46,000	18,00
Vanaelst et al.	2013	Belgium	164	ICP-MS	–	10,000	34,000

ICP-AES inductively coupled plasma atomic emission spectroscopy, *ICP-MS* inductively coupled plasma-mass spectroscopy

*$p<0.0001$, one-tailed *t* test

increases toxicity, heightens damage to cells, and aggravates pathologies (Liu et al. 2014).

The Iraqi public, including the most vulnerable populations of pregnant women and children, may have been cumulatively exposed to metals including Ti and Mg nanoparticles. Such exposures can cause various impairments.

Hair metal studies which relate war-contaminant exposure to neurodevelopmental disorders warrant more research to clarify the effects of war-related pollutants on Iraqi children's health. Registries need to be established to compile and aggregate data from hospitals, clinics, and health centers across the country, including Hawija, Fallujah, and Basra. Data from these registries can then be used to guide researchers in developing large-scale epidemiological studies to determine risk factors, to develop intervention strategies, and to implement plans to protect mother-child health in Iraq. The registries will be instrumental in understanding the impact of birth defects in Iraq.

Exposure to mixtures of chemicals and children's health

In developing fetuses and young children, windows of heightened sensitivity to toxic exposures have long been identified and acknowledged (Goldman 1995). Concurrently, several studies indicate that metals interact to cause health effects which differ from those caused by exposure to individual metals alone. Current literature supports the assertion that exposure to mixtures of metals may have additive or synergistic effects that can alter toxicity, especially in developing children (Claus Henn et al. 2014; Marques et al. 2014). Metals are of particular concern to children's health, because of the relatively high probability of exposure and the ability of metals to individually cause adverse developmental and neurological effects. Interactive effects of early-life lead and manganese exposures on cognition and neurodevelopmental effects have been reported (Claus Henn et al. 2012; Lin et al. 2013). Additionally, a large cohort study has shown interactions between lead and cadmium, with effects on reproductive hormone levels and neurodevelopment (Kim et al. 2013).

Hawija children with neurodevelopmental disorders were exposed to high levels of arsenic. A recent review of the literature offers clear evidence that arsenic exposure can lead to neurodevelopmental problems in children (Parvez et al. 2011). Furthermore, a recent study found significant associations between children's neuropsychological function and hair manganese and arsenic (Rodríguez-Barranco et al. 2013). Thus, metal mixture toxicity is a suspect in the spectrum of neurodevelopmental disorders we observe in Iraqi children living near and around areas contaminated with war-related pollutants.

The small number of recruitable participants for this study has been limiting and can be attributed to the continuous instability in the research area. That instability adds to public's fear, insecurity, and unwillingness to participate in research projects. Nevertheless, the data we offer has been obtained from one of the most hard-to-reach geographical locations, from which no other data is currently available, adding to the strength of this research. Based on our findings, larger-scale public and environmental monitoring of the area, including monitoring of the reproductive health of the local population, is warranted.

Conclusion

Environmental pollutants, like metals, are able to disrupt normal neurodevelopmental processes during periods of heightened sensitivity in children and growing fetuses, thereby causing adverse effects on sensory, motor, and cognitive function. Moreover, multiple metals can interact to cause health effects which are different from those caused by single-metal exposure. Current literature supports the assertion that exposure to mixtures of metals and nanoparticles that can result from high-temperature explosions of war may have additive or synergistic effects that can alter toxicity, especially in developing children. A spectrum of neurodevelopmental disorders are appearing in Iraqi cities where, for over a decade, bombing and military events have led to increased public exposures to toxic metals. To get a clear understanding of the scope of neurodevelopmental disorders in Iraqi children, registries should be set up to compile and aggregate data from hospitals, clinics, and health centers across the country. Data from these registries can then be used to guide researchers in developing large-scale epidemiological studies to determine risk factors, to develop intervention strategies, and to implement plans to protect mother-child health in Iraq.

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